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(54) Title: C-4' MODIFIED ADENOSINE KINASE INHIBITORS

(57) Abstract

This invention relates to adenosine kinase inhibitors and to nucleoside analogs, C-4' modified pyrrolo[2,3-d] pyrimidine and pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention relates to nucleoside analogs of this kind, having zero substitutions or two substitutions at the C-4' position of the furanose (sugar) moiety. The invention also relates to the preparation and use of these adenosine kinase inhibitors in the treatment of cardiovascular, and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.

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C-4' MODIFIED ADENOSINE KINASE INHIBITORS

This invention relates to adenosine kinase inhibitors and to nucleoside analogs, C-4' modified pyrrolo[2,3-d] pyrimidine and pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention relates to nucleoside analogs of this kind, having zero substitutions or two substitutions at the C-4' position of the furanose (sugar) moiety. The invention also relates to the preparation and use of these adenosine kinase inhibitors in the treatment of cardiovascular, and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.

This application is a continuation in part of Serial No. 07/812,916, filed December 23, 1991, which is a continuation-in-part of Serial No. 07/647,117, filed January 23, 1991, which is a continuation-in-part of Serial No. 466,979, filed January 18, 1990, which is a continuation-in-part of Serial No. 408,707, filed September 15, 1989. This application is also a continuation-in-part of Serial No. 08/191,282. The disclosures of these applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Adenosine is an endogenously produced molecule that plays a major role in a variety of important cellular processes. It is a vasodilator, can inhibit immune function, enhance activation of mast cells (associated with allergic reactions), inhibit neutrophil oxygen free-radical production, is antiarrhythmic, and is an inhibitory neurotransmitter. Adenosine is phosphorylated to adenosine triphosphate (ATP) which is used by all cells to store energy for use in future energy-utilizing metabolic reactions or mechanical work (*e.g.* muscle contraction). Extracellular adenosine, frequently prouced by breakdown of intracellular ATP pools, evokes a variety of pharmacological responses through activation of extracellular adenosine receptors located on the surface of nearly all cells. For example, adenosine produces a variety of cardiovascular related effects including vasodilation, inhibition of platelet aggregation, and negative inotropic, chronotropic and domotropic effects on the heart. Adenosine also has effects within the central nervous system (CNS) including inhibition of neurotransmitter release from presynaptic neurons and inhibition of post-synaptic neuron firing in brain and the spinal cord and at sites of inflammation, such as inhibition of neutrophil adhesion to endothelial cells and inhibition of neutrophil oxygen free-radical production.

Compounds that increase extracellular adenosine can be beneficial to living organisms, particularly under certain conditions. For example, compounds that increase adenosine levels have been associated with the treatment of ischemic conditions such as stroke, as well as other conditions benefitted by enhanced adenosine levels, such as inflammation, arthritis, seizures, epilepsy and other neurological conditions. The compounds are also useful for treating pain, as muscle relaxants, and for inducing sleep.

Adenosine kinase is a cytosolic enzyme which catalyzes the phosphorylation of adenosine to AMP. Inhibition of adenosine kinase can potentially reduce the ability of the cell to utilize adenosine, leading to increased adenosine outside of the cell where it is pharmacologically active. However, the regulation of adenosine concentration is complex and involves other adenosine-metabolizing enzymes each with different kinetic properties and mechanisms of regulation. Adenosine can also be deaminated to inosine by adenosine deaminase (ADA) and

condensed with L-homocysteine to S-adenosylhomocysteine (SAH) by SAH hydrolase. The role of each of these enzymes in modulating adenosine concentration is dependent on the prevailing physiological conditions, is tissue specific and is not well understood.

A number of nucleosides including pyrrolo[2,3-d]pyrimidine and pyrazolo[3,4-d]pyrimidine analogs have been evaluated for inhibition of adenosine kinase but were reported to have K_i's of greater than 800 nM. Caldwell and Henderson, Cancer Chemother. Rep., 2:237-46 (1971); Miller et al., J. Biol. Chem., 254:2346-52 (1979). A few compounds have been reported as potent inhibitors of adenosine kinase with K_i's of less than 100 nM. These are the purine nucleosides, 5'-amino-5'-deoxyadenosine (Miller et al.) and 1,12-bis(adenosin-N^6-yl)dodecane (Prescott et al., Nucleosides & Nucleotides, 8:297 (1989)); and the pyrrolopyrimidine nucleosides, 5-iodotubercidin (Henderson et al., Cancer Chemotherapy Rep. Part 2, 3:71-85 (1972); Bontemps et al., Proc. Natl. Acad. Sci. USA, 80:2829-33 (1983); Davies et al., Biochem. Pharmacol., 35:3021-29 (1986)) and 5'-deoxy-5-iodotubercidin (Davies et al., Biochem. Pharmacol., 33:347-55 (1984) and 35:3021-29 (1986)).

Some of these compounds have been used to evaluate whether adenosine kinase inhibition might lead to increased extracellular adenosine concentrations. In rat cardiomyocytes, inhibition of adenosine deaminase by 2'-deoxycoformycin was reported to have no effect on adenosine release from the cells. In contrast, inhibition of ADA together with adenosine kinase by 5'-amino-5'-deoxyadenosine resulted in a 6-fold increase in adenosine release. Zoref-Shani et al., J. Mol. Cell. Cardiol., 20:23-33 (1988). The effects of the adenosine kinase inhibitor alone were not reported. Similar results were reported in isolated guinea pig hearts; in these studies addition of 5'-amino-5'-deoxyadenosine to the perfusion medium, in the presence of EHNA to inhibit deamination, was reported to result in a 15-fold increase of adenosine release. Schrader in Regulatory Function of Adenosine; (Berne et al.) eds. pp. 133-156 (1983). These effects were not apparent in the absence of ADA inhibition, and other studies using isolated rat hearts perfused with 5-iodotubercidin alone, have reported no increase in perfusate adenosine concentration under normoxic conditions Newby et al., Biochem. J., 214:317-323

(1983), or under hypoxic, anoxic or ischemic conditions, Achtenberg et al., Biochem. J., 235:13-17 (1986). In other studies, adenosine release has been measured in neuroblastoma cells in culture and compared with that of a variant deficient in adenosine kinase (AK⁻). The AK cells used in this study were said to release adenosine at an accelerated rate; the concentration of adenosine in the growth medium was reported to be elevated compared to the normal cells. Green, J. Supramol. Structure, 13:175-182 (1980). In rat and guinea pig brain slices, adenosine uptake was reportedly inhibited by the adenosine kinase inhibitors, 5-iodotubercidin and 5'-deoxy-5-iodotubercidin. Davis et al., Biochem. Pharmacol., 33:347-55 (1984). However, inhibition of uptake and intracellular trapping via phosphorylation does not necessarily result in increased extracellular adenosine, since the adenosine could enter other metabolic pathways or the percentage of adenosine being phosphorylated could be insignificant compared to the total adenosine removed.

The effects of adenosine and certain inhibitors of adenosine catabolism, including 5-iodotubercidin were evaluated in an experimental model in which dog hearts were subjected to ischemia and reperfusion; 5-iodotubercidin was reported to have inconsistent effects. Wu, et al., Cytobios, 50:7-12 (1987).

Although the adenosine kinase inhibitors, 5'-amino-5'-deoxyadenosine and 5-iodotubercidin have been widely used in experimental models, the susceptibility of 5'-amino-5'-deoxyadenosine to deamination, and hence its potentially short half life, and the cytotoxicity of 5-iodotubercidin make their clinical utility limited and may limit interpretations based on these compounds. The known pyrrolo[2,3-d]pyrimidines, 5-iodotubercidin and 5'-deoxy-5-iodotubercidin have been reported to cause pronounced general flaccidity and much-reduced spontaneous locomotor activity in mice, interpreted to be skeletal muscle relaxation; to cause hypothermia in mice; and to decrease blood pressure and heart rate in anesthetized rats. Daves et al., Biochem. Pharmacol., 33:347-55 (1984) and 35:3021-29 (1986); and U.S. Patent No. 4,455,420). The skeletal muscle effects of these compounds have been poorly documented, while the other effects were considered significant toxicities.

More recent references concerned with the mechanisms and effects of adenosine kinase inhibitors are Keil et al., Life Sciences 51:171-76 (1992); Zhang et al., J.Pharmacol. Exper. Ther. 264(3): 1415 (1993); Phillis et al., Life Sciences, 53: 497-502 (1993); Sciotti et al., J. Cerebral Blood Flow Metab., 13:201-207 (1993); Pak et al., Soc. for Neuroscience Abs., 20: 149.2 (1994); White, Soc. Neurosci. Abs., 20:308.9 (1994); and Firestein et al., J. Immunology 154:326-34 (1995). These publications in general show that adenosine kinase inhibitors, as a class, have a role in brain functions, and show promise in connection with the treatment of neurological conditions such as seizures. One reference, Phillis et al., indicates that the known adenosine kinase inhibitor 5-iodotubercidin apparently does not protect against ischemic cerebral injury. Keil et al. disclose that adenosine kinase plays a key role in the mediation of nervous system responses to stimulus, particularly pain (antinociception), but notes that the control of endogenous adenosine concentrations by such means is a complex process requiring further study.

Thus, there is a need for selective, potent, and bioavailable adenosine kinase inhibitors with a useful half-life, *i.e.* compounds which can be exploited to beneficially influence or control endogenous adenosine kinase activity, and therefore, extracellular adenosine levels. The compounds of the invention are suitable adenosine kinase inhibitors having these characteristics.

SUMMARY OF THE INVENTION

The invention is directed to novel pyrrolo[2,3-d] pyrimidine or pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors, wherein the furanose moiety has zero substituents or two substituents at the C-4' position. Preferred substitutents are hydroxymethyl, aminomethyl, and methyl. Most preferred are compounds where both substituents are the same, but are not both methyl, or both substituents form a small ring, such as cyclopropyl. In addition to the furanose moiety, additional asymmetric carbons may be present in compounds of the present invention, for example in the substituted heterocyclic pyrrolo[2,3-d] pyrimidine or pyrazolo[3,4-d]pyrimidine ring. All of the resulting isomers, enantiomers, and diastereomers are considered to fall within the scope of the present invention.

These compounds are selective adenosine kinase inhibitors with potencies comparable to or significantly higher than other known adenosine kinase inhibitors. The compounds are also nontoxic, particularly in connection with liver function. The invention concerns the compounds themselves, the preparation of these compounds, and the in vitro and in vivo adenosine kinase inhibition activity of these compounds. Another aspect of the invention is directed to the clinical use of the compounds to increase adenosine concentrations in biological systems. For example, in vivo inhibition of adenosine kinase prevents phosphorylation of adenosine resulting in higher local concentrations of endogenous adenosine.

The compounds of the invention possess advantages for pharmaceutical use such as enhanced pharmacological selectivity, efficacy, bioavailability, ease of manufacture and compound stability.

The compounds of the invention may be used clinically to treat medical conditions where an increased localized adenosine concentration is beneficial. Accordingly, the invention is directed to the treatment of ischemic conditions such as stroke, as well as other conditions benefitted by enhanced adenosine levels, such as inflammation, arthritis, seizures, epilepsy and other neurological conditions. The compounds are also useful for treating pain, as muscle relaxants, and for inducing sleep.

The invention is also directed to prodrugs and pharmaceutically acceptable salts of the compounds described, and to pharmaceutical compositions suitable for different routes of drug administration and which comprise a therapeutically effective amount of a described compound admixed with a pharmacologically acceptable carrier.

Definitions

The following terms generally have the following meanings.

The term "aryl" refers to aromatic groups, which have at least one ring having a conjugated pi electron system, including for example carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are groups wherein all the ring atoms on the aromatic ring are carbon atoms, such as phenyl. Also included are optionally substituted phenyl groups, being preferably phenyl or phenyl substituted by one to three substituents, preferably lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, cyano, perhalo lower alkyl, lower acylamino, lower alkoxycarbonyl, amino, alkylamino, carboxamido, and sulfamido. Further included are phenyl rings fused with a five or six membered heterocyclic aryl or carbocyclic ring, optionally containing one or more heteroatoms such as oxygen, sulfur, or nitrogen.

Heterocyclic aryl groups are groups having from 1 to 4 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like, all optionally substituted.

Optionally substituted furanyl represents 2- or 3-furanyl or 2- or 3-furanyl preferably substituted by lower alkyl or halogen. Optionally substituted pyridyl represents 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl preferably substituted by lower alkyl or halogen. Optionally substituted thienyl represents 2- or 3-thienyl, or 2- or 3-thienyl preferably substituted by lower alkyl or halogen.

The term "biaryl" represents phenyl substituted by carbocyclic aryl or heterocyclic aryl as defined herein, ortho, meta or para to the point of attachment of the phenyl ring, advantageously para; biaryl is also represented as the $-C_6H_4-Ar$ substituent where Ar is aryl.

The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl, picolyl, and the like, and may be optionally substituted.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms. Such groups may be straight chain or branched.

The terms (a) "alkyl amino", (b) "arylamino", and (c) "aralkylamino", respectively, refer to the groups -NRR' wherein respectively, (a) R is alkyl and R' is hydrogen, aryl or alkyl; (b) R is aryl and R' is hydrogen or aryl, and (c) R is aralkyl and R' is hydrogen or aralkyl.

The term "acylamino" refers to RC(O)NR'.

The term "carbonyl" refers to -C(O)-.

The term "acyl" refers to RC(O)- where R is alkyl, aryl, aralkyl, or alkenyl.

The term "carboxamide" or "carboxamido" refers to $-CONR_2$ wherein each R is independently hydrogen, lower alkyl or lower aryl.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups, optionally containing one or more heteroatoms.

The term "alkenyl" refers to unsaturated alkyl groups which contain at least one carbon-carbon double bond and includes straight-chain, branched or cyclic groups, optionally containing one or more heteroatoms such as oxygen, sulfur, or nitrogen.

The term "alkynyl" refers to unsaturated alkyl groups which contain at least one carbon-carbon triple bond and includes straight chain, branched, or cyclic groups, optionally containing one or more heteroatoms such as oxygen, sulfur, or nitrogen.

The term "amidino" refers to $-C(NH)NH_2$.

The term "amidoximo" refers to $-C(NOH)NH_2$.

The term "guanidino" refers to $-NR_1CN(R_2)NR_3R_4$ where R_1, R_2, R_3 and R_4 are independently hydrogen, alkyl or aryl groups.

The term "aminoguanidino" refers to the group $-NR_1NR_2CN(R_3)NR_4R_5$ where R_1, R_2, R_3, R_4 and R_5 are independently hydrogen, alkyl or aryl groups.

The term "ureido" refers to the group $-NR_1C(O)NR_2R_3$ where R_1, R_2 and R_3 are independently hydrogen, alkyl or aryl groups.

The term "carboxylic acid" refers to the group -COOH.

The term "acylguanidino" refers to the group $-C(O)NR_1CN(R_2)NR_3R_4$ where R_1, R_2, R_3 and R_4 are independently hydrogen, alkyl or aryl groups.

The term "mercapto" refers to SH or a tautomeric form thereof.

The term "alkylene" refers to a divalent straight chain or branched chain saturated aliphatic radical.

The term "sulfonamido" means $-SO_2NHR$ where R is hydrogen or lower alkyl.

The term "N-sulfonyl amine" means $-NHSO_2R$ where R is fluoro, lower perfluoroalkyl or lower alkyl.

The term "N-acylated sulfonamide" refers to the group $-SO_2NHCOR$ where R is lower alkyl or lower perfluoroalkyl.

The term "basic nitrogen" generally refers to the nitrogen atom of an alkyl amine and implies a compound whose conjugated acid in aqueous solution has a pKa in the range of 9 to 11.

The term "prodrug" refers to any compound that may have less intrinsic activity than the "drug" but when administered to a biological system generates the "drug" substance either as a result of spontaneous chemical reaction or by enzyme catalyzed or metabolic reaction. Reference is made to various prodrugs such as acyl esters, carbonates, and urethanes, included herein as examples. The groups illustrated are exemplary, not exhaustive and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs fall within the scope of the invention.

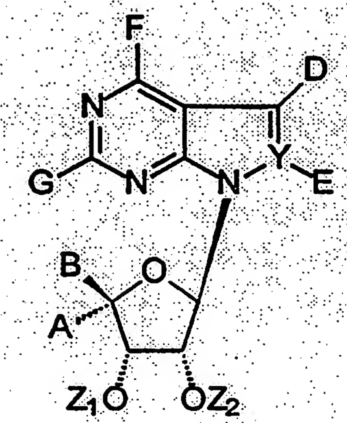
The term "pharmaceutically acceptable salt" includes salts of compounds described herein derived from the combination of a compound of this invention and an organic or inorganic acid. The compounds of the present invention are useful in both free base and salt form. A water solubilizing group is a group that

increases the solubility of an inhibitor by a factor of at least 10 and preferably at least 100 at pH values suitable for intravenous administration (pH 4 to pH 10). In practice the use of salt form amounts to use of base form; both forms are within the scope of the present invention.

The term treatment includes prophylactic or therapeutic administration of compounds of the invention, for the cure or amelioration of disease or symptoms associated with disease, and includes any benefit obtained or derived from the administration of the described compounds.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to C-4'-modified pyrrolo[2,3-d]pyrimidine and pyrazolo[3,4-d]pyrimidine nucleoside analogs of Formula 1, having activity as adenosine kinase inhibitors.



FORMULA 1

wherein:

A and B are both hydrogen, or are each independently alkenyl, the group $(CH_2)_nQ$, where n is from 1 to 4 and Q is hydrogen, hydroxy, alkyl, alkoxy, amino, azido, or halogen; or A and B together form a ring of from 3 to 6 carbons, the ring containing 0 to 3 heteroatoms selected from oxygen and nitrogen and optionally substituted by Q as defined above;

D is halogen, aryl, aralkyl, alkyl, alkenyl, alkynyl optionally containing one or more heteroatoms such as nitrogen, oxygen or sulfur, haloalkyl, cyano, or carboxamido;

E is nothing when Y is nitrogen; and is hydrogen, halogen, or alkyl when Y is carbon;

F is alkyl, aryl, aralkyl, halogen, amino, alkylamino, arylamino, aralkylamino, alkoxy, aryloxy, aralkyloxy, alkylthio, arylthio, aralkylthio;

G is hydrogen or halogen;

Y is carbon or nitrogen;

Z_1 and Z_2 are independently hydrogen, acyl, or taken together form a cyclic carbonate; and pharmaceutically acceptable salts thereof.

Preferably, A and B are the same, but are not both methyl, and most preferably are hydrogen or $(CH_2)_nQ$ where n is 1 and Q is hydroxy, or amino. Also prefered are compounds where A and B form a ring of from 3 to 4 carbons having 0 or 1 heteroatoms. Where A and B are not the same, they are each chosen from the group consisting of methyl, CH_2OH, CH_2OCH_3 and CH_2NH_2. Z is preferably hydrogen, or in prodrug form is preferably acyl or carbonate ester.

D is preferably halogen, heterocyclic aryl, phenyl or substituted phenyl;

E is nothing when Y is nitrogen and is preferably hydrogen when Y is carbon;

G is preferably hydrogen; and

F is halogen, amino, arylamino, or heterocyclic arylamino, most preferably phenylamino or substituted phenylamino. Preferred substitutions are halogen, alkyl, alkoxy, or alkylamino or other groups containing a basic or acidic functionality that improves water solubility. The most preferred substitution is at the para position of phenylamino. For example, prefered compounds of the invention include those where F is phenylamino, substituted at the para position with halogen (*e.g.* fluorine) or a water-solubilizing group.

Exemplary substitutions of the arylamino or phenylamino (Group F) which improve water solubility have the formula $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more nitrogen atoms, N-sulfonylated amino, admidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivative of amidino, guanidino, or aminoguanidino, a heterocyclic aryl group, or a 5 or 6 membered alicyclic ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally substituted by CONVV', where each V is independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms, and optionally oxygen atoms, or V and V' together form a six-membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms. Additionally the water solubilizing groups T can be an anionic

group such as sulfonic acid, carboxylic acid, squaric acid derivatives, 5-tetrazolyl and other bioisosteric replacements of a carboxylic acid group such as, but not limited to, those described in Carini et al, (*J. Med. Chem* 34, 2525 (1991)) and references cited therein. Similar substitutions can also be made at Group D to improve water solubility.

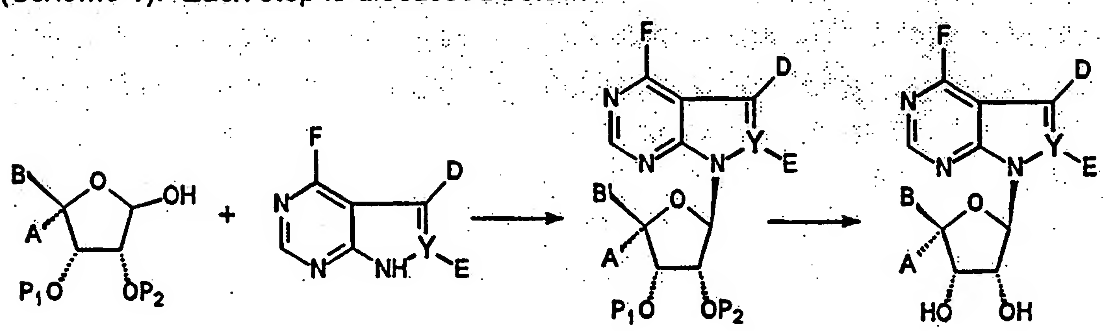
It will be understood that compounds according to the invention, when made according to the methods set forth below, or by other methods, may be provided in both diastereomeric forms. Usually, one form will predominate in the reaction mixture, however, both forms are within the scope of the invention.

Prodrugs of the compounds of the present invention are included in the scope of this application. Such prodrugs may be prepared by esterification of the hydroxyl groups on the sugar ring. Specially preferred will be the ester derivatives that improve the water solubility properties.

SYNTHESIS OF ADENOSINE KINASE INHIBITORS

The compounds of the invention can be made by several reaction schemes. Exemplary synthetic routes are given below.

The synthesis of compounds of the present invention can be viewed as consisting of the following steps: (A) preparation of the carbohydrate **2**, (B) preparation of the heterocycle **3**, (C) coupling of the carbohydrate and the heterocycle to provide a protected intermediate **4**, (D) modification of substituents on the heterocycle and carbohydrate; and (E) removal of the protecting groups (Scheme 1). Each step is discussed below.

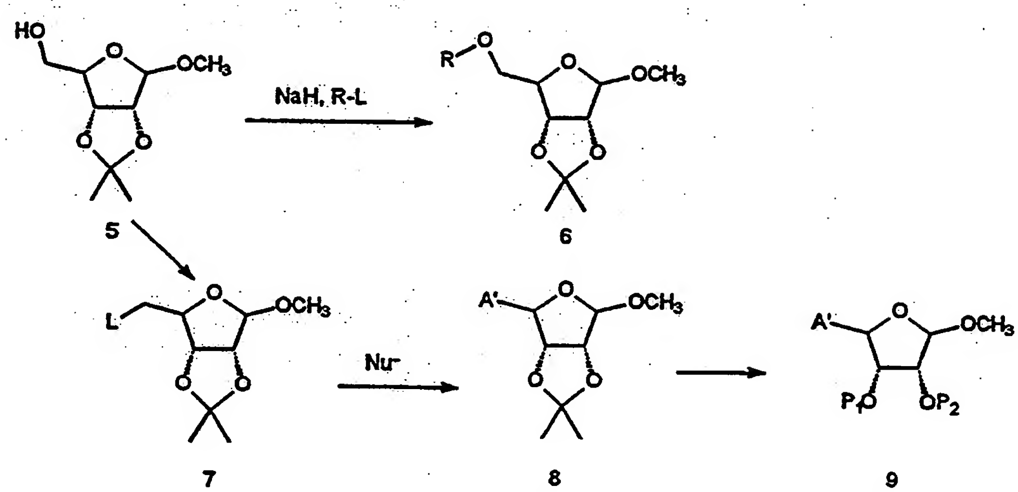


2 3 4 1

SCHEME 1

(A) PREPARATION OF THE CARBOHYDRATE

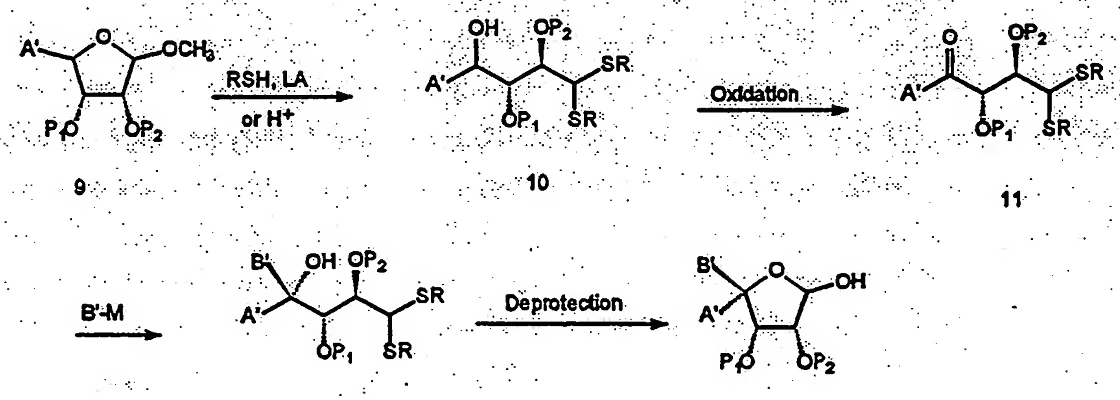
4-substituted carbohydrates of formula **2** are used for the synthesis of compounds of Formula **1**, where A and B are both hydrogen or chosen independently from methyl, azidomethyl, aminomethyl, alkylaminomethyl, alkoxymethyl, hydroxymethyl or alkylthiomethyl. The formula **2** carbohydrates are made from the known methyl 2,3-*O*-methylethylidenefuranoside **5** (Scheme 2). *See*, Leonard N. J. et al. *J. Heterocycl. Chem.* 3, 485 (**1966**). The 5-alkoxy group is introduced to **5**, to make **6**, by the method of Snyder J. R. *et al. Carbohydr. Res.* 163, 169 (**1987**). The 5-deoxy, azido, amino, alkylamino, alkylthio and alternatively alkoxy carbohydrates are made by first transforming the 5-hydroxy into a leaving group L, preferably mesylate, tosylate, trifluoromethanesulfonate or halide. Treatment of **7** with a nucleophile, e.g. hydride, alkylamine, dialkylamine, alkymercaptan, alcohol or other precursors of amines such as azides or protected amines provides intermediates of formula **8**. The isopropylidene is then replaced for less reactive protecting groups, preferably benzyl, according to methods well known to those skilled in the art. For example, Greene T. W., Protective Groups in Organic Chemistry, John Wiley & Sons, New York (**1981**).



SCHEME 2

Carbohydrates for compounds of Formula **1** where A is hydroxymethyl are made by the method of Barker R. *et al. J. Org. Chem.* 26, 4605 (**1961**), to give compounds of formula **9** where A' is preferably benzyl protected hydroxymethyl.

The carbohydrate of Formula **2** is preferably prepared by the method illustrated in Scheme 3. Treatment of methyl glycoside **9** with a thiol or a dithiol, preferably 1,3-propanedithiol, in the presence of an acid or a Lewis acid, preferably boron trifluoride-diethyletherate, gives dithioacetal **10**. Oxidation of the generated alcohol using well described methods and reagents, e.g. pyridinium dichromate, pyridinium chlorochromate, Moffat oxidation, sulfur trioxide-pyridine, preferably Swern oxidation, gives ketone **11**. Chelation-controlled addition of an organometallic B'-M, preferably organolithium, stereoselectively provides tertiary alcohol **12**. The dithioacetal protecting group is removed using a modification of the procedure developed by Fetizon M. *et al. J. Chem. Soc. Chem. Comm. 382* (**1972**), involving treatment of thioacetal with iodomethane and an inorganic base, preferably calcium carbonate. Alternatively, other dithioacetal deprotection procedures are known which use reagents such as *N*-halosuccinimide, cupric, mercuric and silver salts. However the use of these oxidative procedures is precluded for compounds bearing incompatible functional groups such as thioethers, azides or amines.

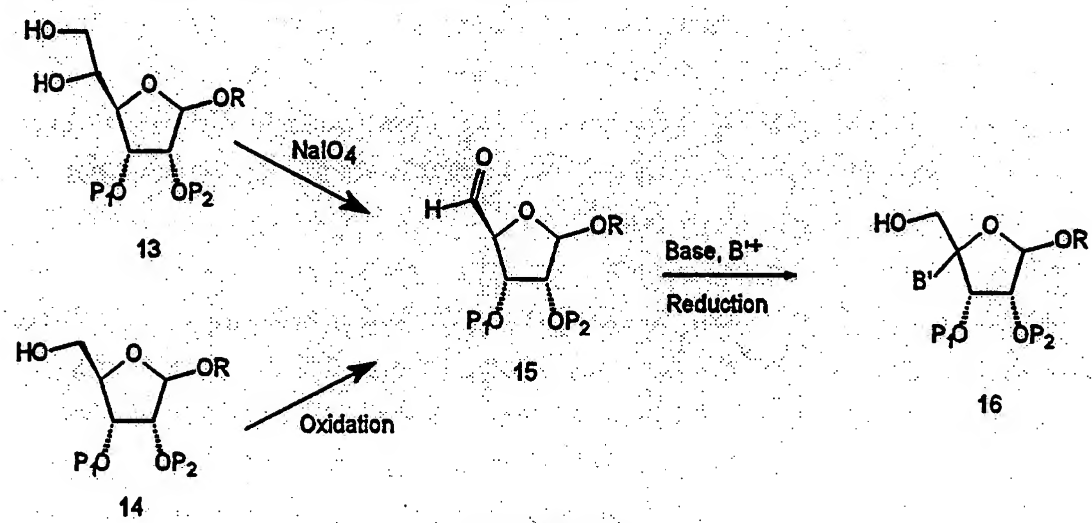


9 10 11 12 2

SCHEME 3

Alternatively the second 4-C-substituent may be introduced using the procedure of Youssefyeh R. D. *et al. J. Org Chem.* 44(8), 1301(**1979**) where alkylation of an aldehyde of formula **15** with electrophile B'+ followed by a reduction gives compound **16** (Scheme 4). The aldehyde is obtained from the oxidative cleavage, preferably with sodium periodate, of hexofuranose **13** or oxidation of the

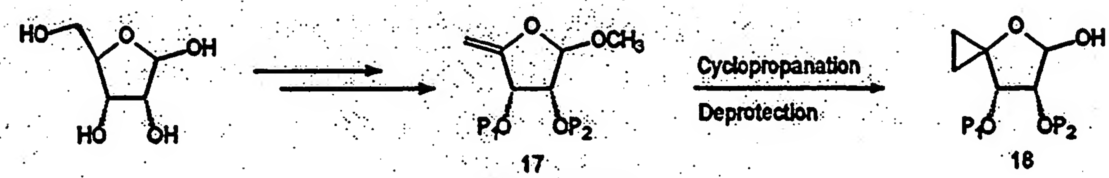
primary alcohol of furanoside **14**, preferably using a Moffat oxidation. Another method to obtain compounds of formula **(16)** is to use the procedure of Johnson C. R. *et al. J. Org Chem.* 59(20), 5854 **(1994)**.



SCHEME 4

Carbohydrates for compounds of Formula **1** where A=B=H are made using a suitably protected carbohydrate of formula **2** where A'=B'=H. This carbohydrate is easily obtained from erythrofuranose according to methods well known to those skilled in the art described in Greene T. W., *Protective Groups in Organic Chemistry*, John Wiley & Sons, New York **(1981)**. This carbohydrate is also easily obtained by reduction of the corresponding lactone as in N. Cohen *et al. J. Am. Chem.Soc.* 105, 3661, **(1983)**.

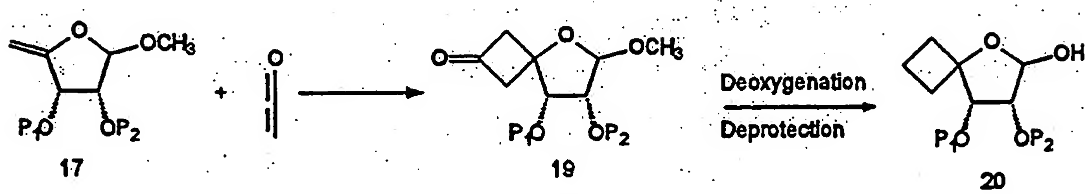
Carbohydrates of formula **2**, where A and B form a ring, e.g. cyclopropyl, are prepared from D-ribose via the well known enol ether **17** (Scheme 5). Inokawa S. *et al. Carbohydr. Res.* 30, 127 **(1973)**. Cyclopropanation is performed according to the procedure of Simmons H.E. *et al. J. Am Chem. Soc.* 81, 4256 **(1959)** or one of its many modifications. Alternatively cyclopropanation is accomplished with a diazoalkane and a metal salt, preferably palladium. Cossy J. *et al. Tetrahedron Lett.* 28(39), 4547 **(1987)**.



SCHEME 5

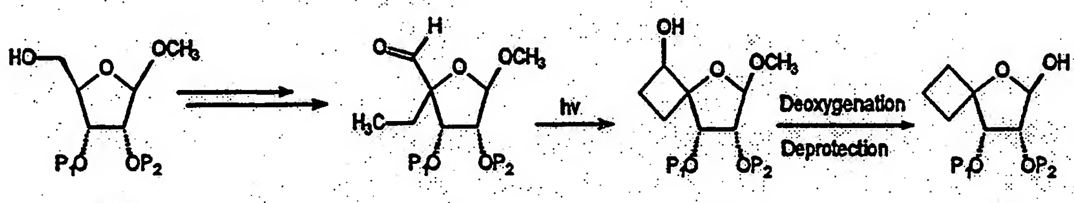
Another alternative is to generate a carbene from a dihaloalkane or trihalomethane with a base in the presence of the olefin (Von E. Doering W. *et al. J. Am. Chem. Soc.* 76, 6162 (**1954**)) followed by dehalogenation, for example according to Jefford C. W. *et al. J. Am. Chem. Soc.* 94, 8905 (**1972**). Cycloaddition between diazomethane and compounds of formula **17** provides a pyrazoline intermediate which upon photolysis and deprotection produces spirocyclopropane **18** (Samano V. *et al. Tetrahedron Lett.* 35(21), 3445 (**1994**)). The deprotection of the anomeric center is in turn accomplished using one of the many procedures well known to those skilled in the art, *e.g.* Greene, T. W., Protective Groups in Organic Chemistry, John Wiley & Sons, New York, (**1981**).

Carbohydrates of formula **20** are made by a wide variety of procedures. Reaction of olefin **17** with ketene under the conditions of Redlich H. *et al. Angew. Chem.* 101(6), 764 (**1989**) gives cyclobutanone **19** (Scheme 6), with is then deoxygenated using the procedure of Mori K. *et al. Tetrahedron*, 43(10), 2229 (**1987**) or Romming C. *et al. Acta Chem. Scan. B*, 40(6), 434 (**1986**). The free reducing sugar is then obtained as mentioned above (Greene T. W. *Protective Groups in Organic Chemistry* John Wiley & Sons, New York, **1981**).



SCHEME 6

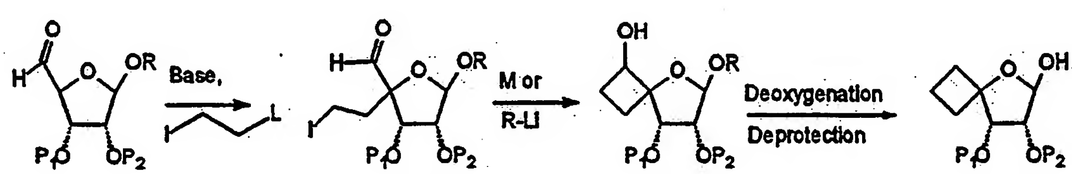
An alternative route uses the photochemical cyclization of a carbohydrate of formula **22** to give cyclobutanol **23** (Scheme 7, Paquette L. A. *et al. J. Am. Chem. Soc.* 108(13), 3841 (**1986**). Deoxygenation of alcohol **23** occurs according to the procedure of Barton D. H. R. *et al. Pure Appl. Chem.* 53, 15 (**1981**). Precursor **22** is made by 4-alkylation of the corresponding aldehyde derived from selectively protected methyl riboside **21**, *e.g.* Youssefyeh R. D. *et al. J. Org Chem.* 44(8), 1301 (**1979**).



21 22 23 20

SCHEME 7

Alkylation of aldehyde **15** with a two carbon dielectrophile, preferably diiodoethane, gives 4-disubstituted aldehyde **24** (Scheme 8, Youssefyeh R. D. *et al. J. Org Chem.* 44(8), 1301 (**1979**)). Treatment of aldehyde **24** with a metal or metal salt, preferably samarium diiodide (Molander G. A. *et al. J. Am. Chem. Soc.* 109(2), 453 (**1987**)), or with an organometallic reagent, preferably an alkyllithium (Vanderdoes T. *et al. Tetrahedron Lett.* 27(4), 519 (**1986**)), achieves the ring closure. The cyclobutanol is then deoxygenated and deprotected at the anomeric position using the procedures previously mentioned to provide spirocyclobutylfuranose **20**.



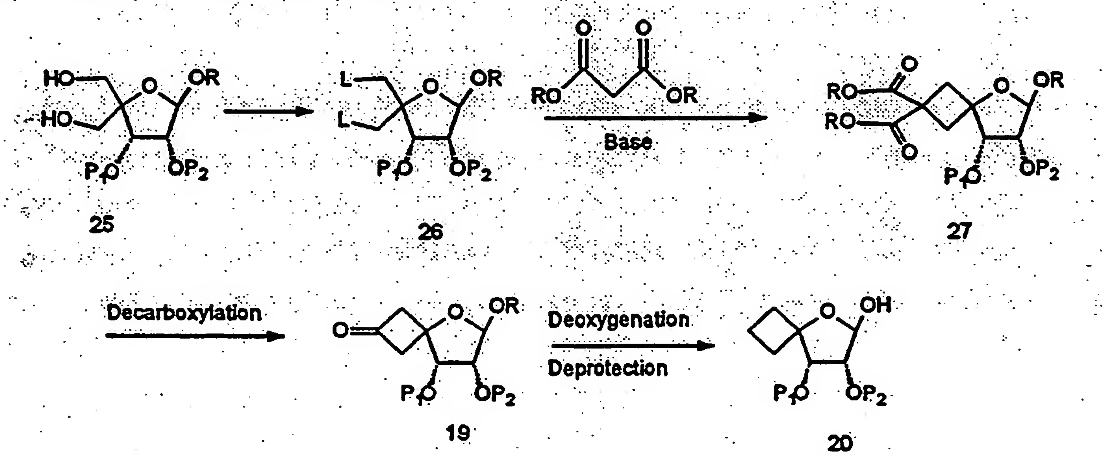
15 24 23 20

SCHEME 8

An alternative method to make carbohydrate of formula **20** is illustrated in Scheme 9. Activation of the two primary hydroxyl groups using the many procedures well known to those skilled in the art (Larock R. C. *Comprehensive*

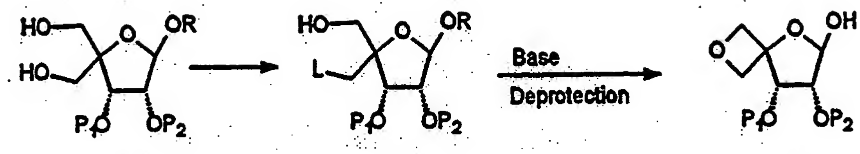
Organic Transformations, VCH Publishers, Inc. New York (1989)) followed by dialkylation with a malonate produces dicarboxylate spirocyclobutane **27** (Pecquet P. *et al. Heterocycles* 34(4), 739 (1992)). Decarboxylation using the procedure of Tufariello J. J. *et al. Tetrahedron Lett.* 6145 (1966) followed by deoxygenation and deprotection of cyclobutanone **19** as previously mentioned gives spirocyclobutane **20**.

Carbohydrate of formula **29** is made by activation of one of the primary hydroxyl groups of diol **25** (Scheme 10, Larock R. C. *Comprehensive Organic Transformations*, VCH Publishers, Inc. New York, (1989)). Cyclization occurs upon treatment of alcohol **28** with a base (Koll P. *et al. Angew. Chem. Int. Ed. Engl.* 25, 368 (1986)). The anomeric position is then deprotected as previously mentioned to afford spirooxetanofuranose **29**.



SCHEME 9

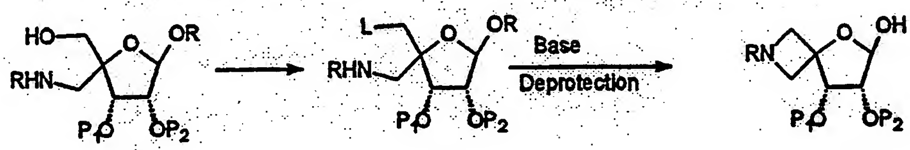
Alternatively, compound **29** is obtained via Mitsunobu reaction of diol **25** under the conditions of Berkowitz W. F. *et al. J. Org. Chem.* 52(6), 1119 (1987) which gives compound **29** after deprotection. As another alternative, lithium chloride treatment of a cyclic carbonate derived from diol **25** followed by deprotection also gives carbohydrate **29**.



25 28 29

SCHEME 10

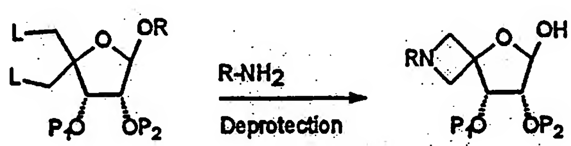
The syntheses of the carbohydrates of formula **32** are illustrated in Schemes 11, 12 and 13. Treatment of activated carbohydrate **31** with a base prior to deprotection gives spiroazetidinofuranose **32** (Scheme 11, Vaughan W. R. *et al.* *J. Org. Chem.* 26, 138 (1961)). Aminoalcohol **30** is prepared following the procedures used to make carbohydrates of formula **2** (Scheme 3).



30 31 32

SCHEME 11

Alternatively, treatment of diactivated compound **26** with ammonia, a primary amine, a protected amine or an activated amine (Scheme 12) followed by deprotection gives carbohydrate **32**. *See,* Juaristi E. *et al. Tetrahedron Lett.* 25(33), 3521 (1984).

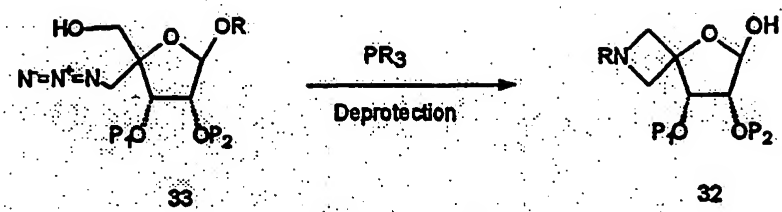


26 32

SCHEME 12

An other alternative is to treat azidoalcohol **33** with a trialkyl or triaryl phosphine (Scheme 13, Szmuszkovicz J. *et al. J. Org. Chem.* 46(17), 3562 (1981)).

Decomposition of the azido group and Mitsunobu like cyclization gives after deprotection azetidine **32**.

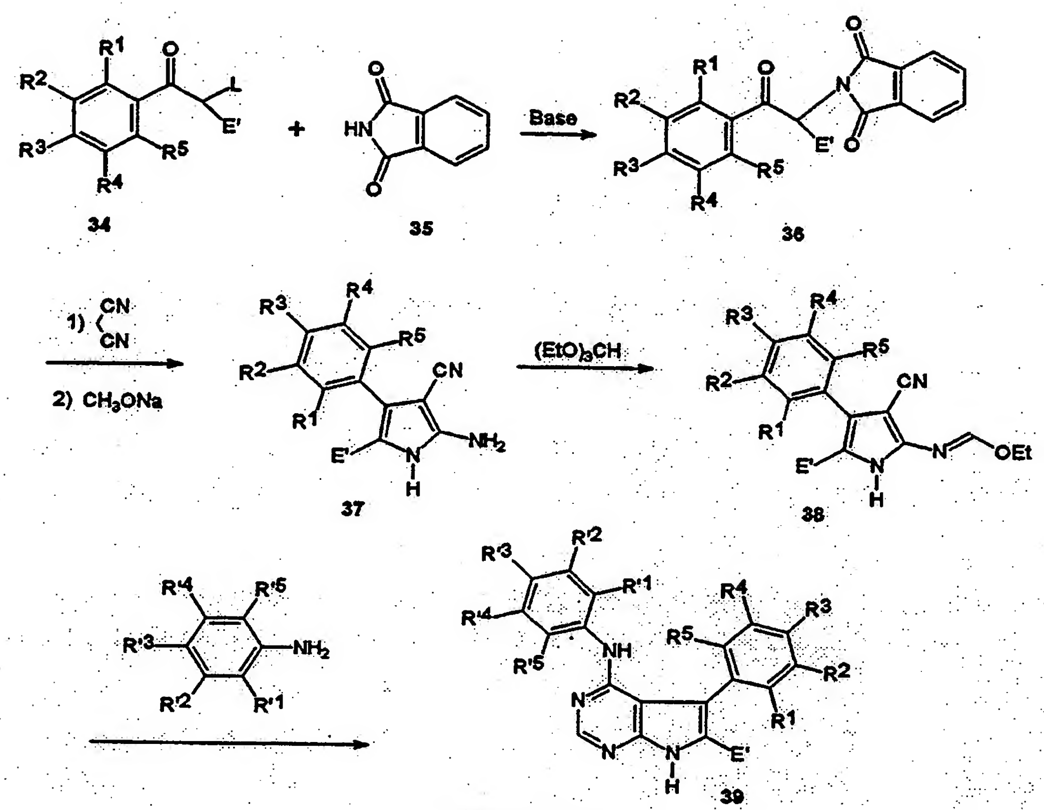


SCHEME 13

(B) PREPARATION OF THE HETEROCYCLE

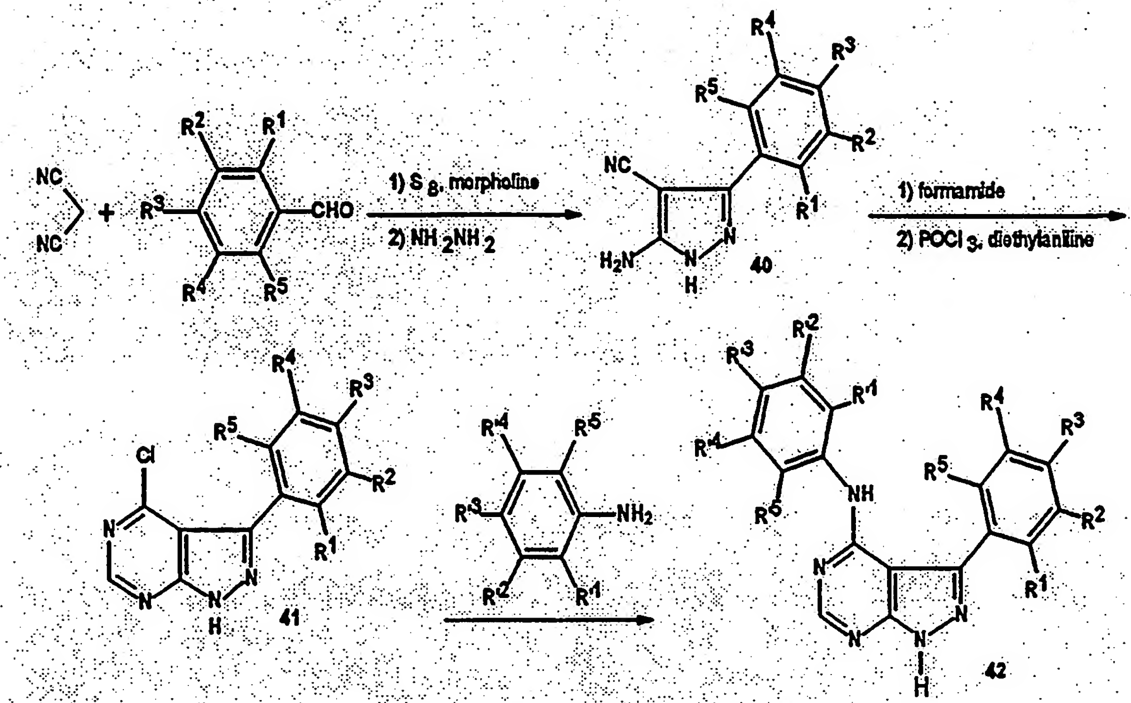
Heterocycles for compounds of formula **1** (Scheme 1) where Y=C, F' and D' are substituted aromatic groups, preferably para-fluorophenyl, G is hydrogen, and E' is a hydrogen, alkyl, preferably hydrogen, are made via a pyrrole intermediate **37** made using the procedure of Gewald, K. Z. *Chem.*, 1, 349 (**1961**). Alternatively, **37** is made by condensing phenone **34**, where L is halide or sulfonate, with phthalimide **35** in order to introduce the pyrrole nitrogen. Knoevenagel condensation of ketone **36** with malonitrile followed by removal of the phthalimide protecting group affords pyrrole **37**.

Upon treatment with an orthoester, preferably triethylorthoformate, an imidate is formed which is further condensed with a substituted aniline, preferably *para*-fluroaniline, to give diaryl-pyrrolopyrimidine **39** (Taylor, E. C. *et al. J. Am Chem. Soc.* 87(9),1995 (**1965**)). Additionally, the pyrrolopyrimidine can be further functionalized at the 6 position, when E' is methyl, by treatment with *N*-bromosuccinimide (Saroja ,B. *et al. Tetrahedron Lett* **1984**, 25(47), 5429). Treatment of this bromomethylene with a nucleophile or with an alkyllithium and an electrophile allows easy introduction of functional groups such as amino or guanidino.



SCHEME 14

Heterocycles for compounds of formula **1** (Scheme 1) where Y=N, F' and D' are substituted aromatic groups, preferably *para*-fluorophenyl.



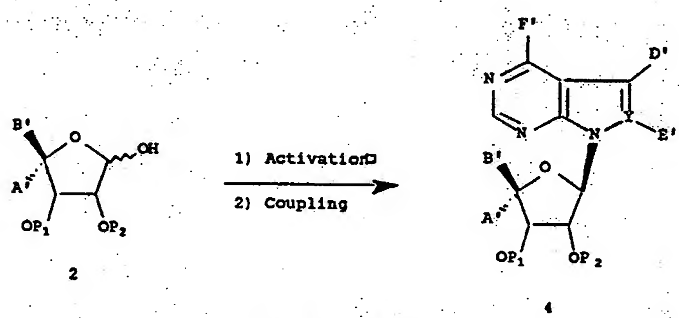
SCHEME 15

Compounds where E is "nothing" are made using the procedure of Kobayashi, S. *Chem. Pharm. Bull. (Japan)* 21, 941 (1973). Knoevenagel condensation of malonitrile with a substituted benzaldehyde, preferably *para*-fluorobenzaldehyde, followed by treatment with hydrazine gives 5-aminopyrazole-4-carbonitrile **40** (Scheme 15). The 4-chloro-pyrazolo[3,4-d]pyrimidine **41** is obtained upon ring closure reaction with formamide and chlorination using the procedure described by Cheng, C. C. *J. Org. Chem.* 21, 1240 (1966). Treatment of chloride **41** with ammonia, for the 4-amino series, or a substituted aniline preferably *para*-fluoroaniline, as previously mentioned gives diarylpyrazolopyrimidine **42**.

C. <u>COUPLING OF THE CARBOHYDRATE WITH THE HETEROCYCLE</u>

The coupling of the carbohydrate **2** with pyrrolo[2,3-d]pyrimidine heterocycles is accomplished as follows (Scheme 16). The sugar is first converted to its 1-halo derivative, preferably chloro, by reacting it with CCl_4 and HMPT by a procedure described in Wilcox, C. T. *et al. Tetrahedron Lett.* 27(9), 1011 (1986). The halo derivative is condensed with the anion of the heterocycle **3** (where Y is carbon

and E is hydrogen) using a phase transfer catalyst such as TDA-1. Rosemeyer H., and Seela, F, Helvetica Chimica Acta, 71:1573 (1988). The resulting blocked nucleosides are deprotected by a variety of procedures well known to those skilled in the art.



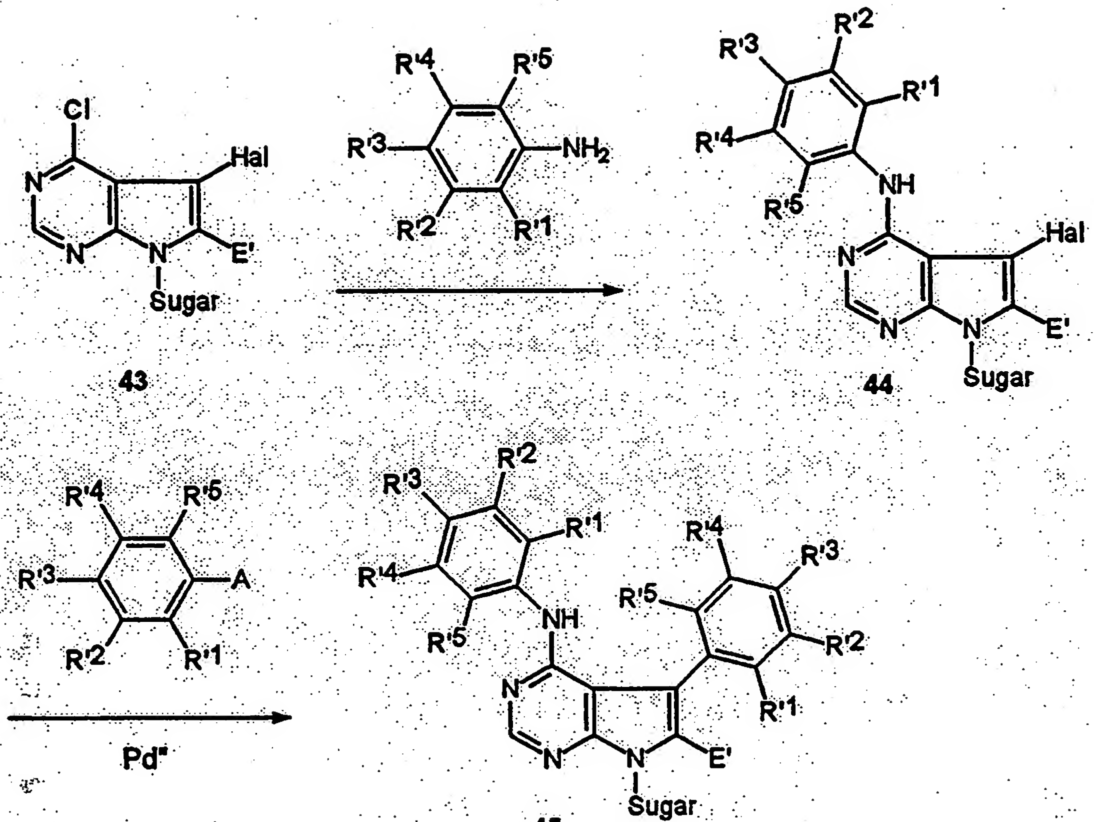
SCHEME 16

Coupling of sugars to the pyrazzolo[3,4-d]pyrimidine bases is performed by Lewis acid catalysis conditions. Cottom, et al., J. Med. Chem., 27, 11210 (1984). In such cases the sugars are converted to their 1-O-acyl form, preferably 1-O-acetyl, by again using one of the many standard acetylation procedures. A mixture of the heterocycle **3** (where Y is nitrogen) and the acetylated sugar in boiling nitromethane is treated with boron trifluoride diethyl etherate. The products are purified by chromatography or crystallization, and are deprotected to obtain the final compounds.

D. MODIFICATION OF SUBSTITUENTS ON THE HETEROCYCLE

Due to the chemical incompatibility between some of the substituents on the heterocycle and the glycosidation-reaction conditions, the final functionalization of the nucleoside is done after the coupling reaction. For example, the 5-aryl group is introduced onto the pyrrolopyrimidine ring system using one of the many palladium-catalyzed cross coupling procedures (review: Stille, J. K. *Ang. Chem., Int. Ed. Engl.* 25, 508(1986)).

Typically, a 4-substituted-amino-5-halopyrrolo[2,3-d]pyrimidine **44**, where the halogen is iodo, is coupled to an arylboronic acid (*i.e.* A=$B(OH)_2$ in Scheme 17) in the presence of a catalyst such as tetrakistriphenylphosphine palladium.

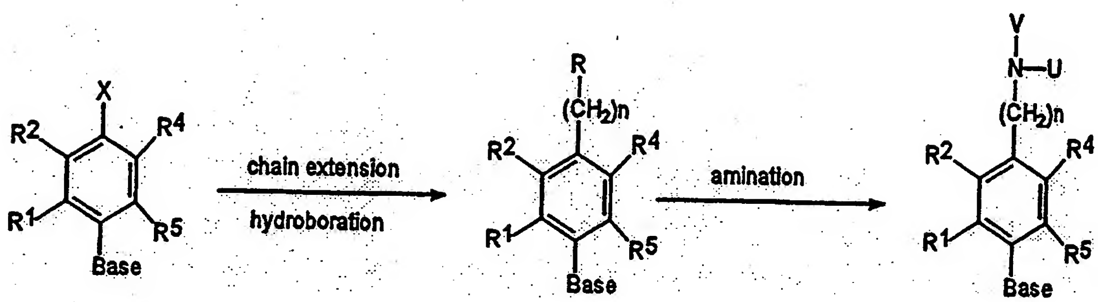


43 44 45

SCHEME 17

Alternatively, in place of aryl boronic acids, other activated aryl compounds such as aryltrialkyltin(A=Sn(alkyl)$_3$ is successfully used to obtain the final product **45**. Substitution of the aryltrialkyltin by an unsaturated trialkyl stannane by procedures as described but not limited to the one described in Stille, J. K. *Ang. Chem.. Int. Ed. Engl.* 25, 508 (1986) provides the 5-alkenyl derivative which can be hydrogenated in order to prepare the corresponding alkyl analog.

Further modifications can be added to the aromatic rings after cross coupling with the heterocycle either before or after glycosidation. Reduction, oxidation and/or deprotection steps are done at this stage. For instance a cyano group is oxidized to its carboxamide or reduced to its amine. A *N*-phenylacetamide is deprotected and kept as its aniline or transformed to its trifluoromethanesulfonamide to improve water solubility.



45 46 R=OH 47 R=L 48

SCHEME 18

Carbon chain extension is done at this stage (Scheme 18). The aromatic ring substituent on the glycosilated intermediate **45** where X is halide or trifluoromethanesulfonate is coupled with a vinyl or allyl trialkyltin species using one of the many palladium-catalyzed cross coupling procedures (review: Stille, *supra*). The double bond is then oxygenated at the terminal position and the resulting alcohol **46** is converted to a leaving group L, preferably iodide (Srivastava, P. C. et al. J. Med Chem. 1975, 18(12), 1237). Displacement by an amine completes the carbon chain extension and improves the water solubility for compounds of formula **48**.

Other potential water solubilizing groups such as guanidino derivatives can be prepared from the corresponding amino or hydroxy compounds by application of methods described in the literature such as, but not limited to, the procedures described by Miller and Bischoff (*Synthesis* 778 (**1986**)), Dodd and Kozikowski (*Tetrahedron Lett.* 35, 977 (**1994**)), Beatty and Magrath (*J. Chem. Soc.* 12 (**1965**)), Larson et al (*Int. J. Pept. Protein Res.* 9, 182(**1977**)), Brand and Brand (Org. Synth. 22, 59 (**1942**)), Ichikawa (*Tetrahedron Lett* 29, 4957(**1988**)), Katritzky et al (*Synth. Commun.* 25, 1173 (**1995**)), Ariga and Anslyn (*J.Org. Chem.* 57, 417 (**1992**)), Palát et al (*Collect. Czech. Chem. Commun.* 57, 1127 (**1992**)) or M. S. Bernatowicz (*J. Org. Chem.* 57, 2497 (**1992**). Acylguanidines can be prepared by methods described in the literature such as the methods described by Bock et al (*J. Med.Chem.* 29, 1540 (**1986**)) and references cited therein.

E. REMOVAL OF THE PROTECTING GROUPS

Acid labile protecting groups such as ketals, silyl ethers or ethers are removed using a dilute acid or a weak organic acid, e.g. 0.1N hydrochloric acid or 70% aqueous trifluoroacetic acid (Greene, T. W., Protective Groups in Organic Chemistry, John Wiley & Sons, New York (1981). Base labile protecting groups such as acyls or carbamates are removed by treatment with an organic or inorganic base, e.g. sodium methoxide, sodium hydroxide, ammonia (*Id*). Benzyl protecting groups are removed by hydrogenolysis in the presence of a metal catalyst, preferably palladium chloride. Shen, T. Y. *et al. J. Org. Chem.* 30, 835 (1965).

Preferred compounds of the invention, which can be made using the methods described, include the following.

EXAMPLES

Example 1 Preparation of compound of formula 10

2,3,5-Tri-O-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

Boron trifluoride diethyl etherate (11.4 mL, 92.4 mmol) was added to a solution of methyl 2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranoside (30 g, 66 mmol) (Barker, R. and Fletcher, H. G. *J. Org. Chem.* 1961, *26*, 4605) and 1,3-propanedithiol (10 mL, 99 mmol) in dry dichloromethane (130 mL) at –48° C. The reaction mixture was stirred 30 minutes at –48° C and warmed to room temperature in the course of one hour. After stirring at room temperature for one hour, the mixture was quenched with saturated aqueous sodium bicarbonate, diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 90/10 to 75/25). Yield 31.9 g, 94 %, Rf = 0.3 (silica gel, hexanes/ethyl acetate 80/20).

Example 2 Preparation of compound of formula 11

(3S, 4R)-1,3,4-Tri-[(phenylmethyl)oxy]-5-(1,3-dithian-2-yl)pentan-2-one

A solution of dimethyl sulfoxide (22.1 mL, 312 mmol) in dry dichloromethane (100 mL) was added dropwise over 10 minutes to a solution of oxalyl chloride (16.3 mL, 187 mmol) in dry dichloromethane (200 mL) at -78°C. After stirring 10 minutes at -78°C, a solution of the compound of Example 1 (31.9 g, 62.4 mmol) in dry dichloromethane (100 mL) was added dropwise to the reaction mixture over 20 minutes at -78°C. After stirring at -78°C for 20 minutes, a solution of triethylamine (87 mL, 624 mmol) in dry dichloromethane (100 mL) was added dropwise over 10 minutes at -78°C. After completion of the addition the internal temperature was allowed to raise to -40°C over 30 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was back extracted twice with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 90/10 to 70/30). Yield: 27.9 g, 88 %, Rf = 0.35 (silica gel, hexanes/ethyl acetate 80/20).

Example 3 Preparation of compound of formula 12

4-C-[(Phenylmethyl)oxy]methyl-2,3,5-tri-*O*-phenylmethyl-1-(1,3-dithian-2-yl)-D-*ribo*-pentane.

A solution of the compound of Example 2 (1 g, 1.97 mmol) in dry tetrahydrofuran (25 mL) was added dropwise over 5 minutes to a solution of [(phenylmethyl)oxy]methyllithium (3.94 mmol) (Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481) in dry tetrahydrofuran (25 mL) at -78°C. After stirring for 20 minutes at -78°C, the reaction mixture was quenched with saturated aqueous ammonium chloride, warmed to room temperature, diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 90/10 to 75/25). Yield: 1.05 g, 85 %, Rf = 0.45 (silica gel, hexanes/ethyl acetate 70/30).

Example 4 Preparation of compound of formula 2

4-*C*-[(Phenylmethyl)oxy]methyl-2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranose

A heterogeneous mixture of calcium carbonate (4 g, 40 mmol), iodomethane (1.25 mL, 20 mmol) and the compound of Example 3 (2.52 g, 4 mmol) in acetonitrile/tetrahydrofuran/water (1/1/9, 44 mL) was refluxed overnight (Fetizon, M. *J. Chem. Soc., Chem. Comm.* 1972, 382). More iodomethane (1.25 mL, 20 mmol) was added and refluxing was pursued for 24 hours. The mixture was cooled, diluted with ethyl acetate and washed with saturated aqueous sodium chloride. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 80/20 to 65/35). Yield: 2.06 g, 95 %, Rf = 0.2 (silica gel, hexanes/ethyl acetate 70/30).

Example 5 Preparation of compound of formula 4

4-*N*-Phenylamino-5-phenyl-7-(4-*C*-[(phenylmethyl)oxy]methyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine

Hexamethylphosphorous triamide (415 µL, 1.95 mmol) was added to a solution of carbon tetrachloride (250 µL, 2.6 mmol) and the compound of Example 4 (349 mg, 0.65 mmol) in dry toluene at -78° C. The reaction mixture was warmed to 0°C in the course of one hour and stirred at 0° C for 30 minutes. The orange solution was quenched with water, diluted with toluene and washed with water and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to a volume of c.a. 5 mL. The chloro-sugar solution was added to a mixture of 4-*N*-phenylamino-5-phenyl-pyrrolo[2,3-*d*]pyrimidine (370 mg, 1.3 mmol), finely powdered potassium hydroxide (85%, 170 mg, 2.6 mmol), tris[2-(2-methoxyethoxy)ethyl]amine (420 µL, 1.3 mmol) and 4 Å molecular sieves in dry toluene which had been stirring at room temperature for 2 hours. After stirring overnight at room temperature, the reaction mixture was filtered through Celite® and the filtering pad was rinsed with ethyl acetate. The filtrate was diluted with ethyl acetate and washed with saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

(hexanes/ethyl acetate 90/10 to 70/30). Yield: 229 mg, 44 %, Rf = 0.6 (silica gel, hexanes/ethyl acetate 80/20).

Example 6 Preparation of compound of formula 1
4-*N*-Phenylamino-5-phenyl-7-(4-*C*-hydroxymethyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine: Table 1 #1

A mixture of palladium hydroxide (200 mg) and 4-*N*-phenylamino-5-phenyl-7-(4-*C*-[(phenylmethyl)oxy]methyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (212 mg, 0.26 mmol) in acetic acid/ methanol (1/1, 10 mL) was vigorously stirred at room temperature under one atmosphere of hydrogen. After 7 days of stirring the reaction mixture was filtered through Celite® and the filtering pad was rinsed with hot methanol. The filtrate was concentrated under reduced pressure and the solid residue was recrystallized from ethanol. Yield: 30 mg, 25 %, Rf = 0.4 (silica gel, dichloromethane/methanol 80/20), mp 232° C.

Example 7 Preparation of compound of formula 10
5-Deoxy-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

The title compound was synthesized following a procedure analogous to the synthesis described in Example 1. Thus methyl 5-deoxy-2,3-di-*O*-(phenylmethyl)-D-ribofuranoside (7 g, 21.3 mmol) prepared by a procedure analogous to the synthesis of methyl 2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranoside (Barker, R. and Fletcher, H. G. *J. Org. Chem.* **1961**, *26*, 4605), gave 7.9 g, 92 %, Rf = 0.35 (silica gel, hexanes/ethyl acetate 70/30).

Example 8 Preparation of compound of formula 11
(3S,4R)-3,4-Bis-[(phenylmethyl)oxy]-5-(1,3-dithian-2-yl)pentan-2-one

The title compound was synthesized following a procedure analogous to the synthesis described in Example 2. Thus the compound of Example 7 (7.9 g, 19.5 mmol) gave 6.32 g, 80 %, Rf = 0.2 (silica gel, hexanes/ethyl acetate 70/30).

Example 9 Preparation of compound of formula 12

5-Deoxy-4-*C*-methyl-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

A solution of the compound of Example 8 (2 g, 5 mmol) in dry tetrahydrofuran (30 mL) was added dropwise over 10 minutes to a solution of methyllithium (20 mmol) in dry tetrahydrofuran (20 mL) at -78° C. After stirring for 20 minutes at -78° C, the reaction mixture was quenched by slow addition of a solution of acetic acid (2 mL) in dry tetrahydrofuran (10 mL) over 5 minutes at -78° C. The quenched solution was warmed to room temperature, diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 85/15 to 75/25). Yield: 2.038g, 98 %, Rf = 0.38 (silica gel, hexanes/ethyl acetate 70/30).

Example 10 Preparation of compound of formula 2

5-Deoxy-4-*C*-methyl-2-3-di-*O*-(phenylmethyl)-D-ribofuranose

The title compound was synthesized following a procedure analogous to the synthesis described in Example 4. Thus, the compound of Example 9 (2.04 g, 4.87 mmol) gave 1.4 g, 88 %, Rf = 0.4 (silica gel, hexanes/ethyl acetate 70/30).

Example 11 Preparation of compound of formula 2

5-Deoxy-4-*C*-methyl-2,3-*O*-(methylethylidene)-D-ribofuranose

A mixture of palladium hydroxide (0.5 g) and the compound of Example 10 (2.62 g, 7.98 mmol) was vigorously stirred at room temperature for 3 hours under one atmosphere of hydrogen. The reaction mixture was filtered through Celite® and the filtering pad was rinsed with hot methanol. The filtrate was concentrated under reduced pressure and azeotroped twice with dimethylformamide. The residue was dissolved in dimethylformamide (10 mL). *p*-Toluenesulfonic acid monohydrate (catalytic) and 2,2-dimethoxypropane (4.6 mL, 32 mmol) were added. After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated

under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 80/20 to 70/30). Yield: 507 mg, 34 %, Rf = 0.3 (silica gel, hexanes/ethyl acetate 70/30).

Example 12 Preparation of compound of formula 4
4-*N*-Phenylamino-5-phenyl-7-(5-deoxy-4-*C*-methyl-2,3-*O*-(methylethylidene)-β-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine

Hexamethylphosphorous triamide (800 μL, 4.35 mmol) was added to a solution of carbon tetrachloride (600 μL, 5.8 mmol) and the compound of example 11 (272 mg, 1.45 mmol) in dry toluene at -50° C. The reaction mixture was warmed to -10° C in the course of 30 minutes and stirred at -10° C for 15 minutes. The orange solution was quenched with water, diluted with toluene and washed with water and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to a volume of c.a. 5 mL. The chloro-sugar solution was added to a mixture of 4-*N*-phenylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (830 mg, 2.9 mmol), finely powdered potassium hydroxide (85%, 380 mg, 5.8 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (925 μL, 2.9 mmol) in dry toluene which had been stirring at room temperature for 90 minutes. After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 70/30 to 50/50). Yield: 223 mg, 34 %, Rf = 0.3 (silica gel, hexanes/ethyl acetate 60/40).

Example 13 Preparation of compound of formula 1
4-*N*-Phenylamino-5-phenyl-7-(5-deoxy-4-*C*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine

A solution of 4-*N*-phenylamino-5-phenyl-7-(5-deoxy-4-*C*-methyl-2,3-*O*-(methylethylidene)-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (220 mg) in 70 % aqueous trifluoroacetic acid (20 mL) was stirred at 0° C for one hour and at room temperature for one hour. The reaction mixture was concentrated under reduced pressure and azeotroped twice with water and twice with ethanol. The residue was

neutralized with saturated aqueous sodium bicarbonate and the precipitated nucleoside was filtered and rinsed with water. The solid was recovered and recrystallized from ethanol. Yield: 130 mg, 65 %, Rf = 0.5 (silica gel, dichloromethane/methanol 90/10), mp 198-200°C.

Example 14 Preparation of compound of formula 18

Methyl 2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-D-erythrofuranoside

A solution of methyl 5-deoxy-2,3-*O*-(methylethylidene)-β-D-*erythro*-pent-4-enofuranoside (2 g, 10.7 mmol) (Inokawa, S. *et al. Carbohyd. Res.* **1973**, *30*, 127) and diodomethane in dry ether (20 mL) was added dropwise over 4 hours to a refluxing suspension of freshly made zinc-copper couple in dry ether. The reaction mixture was refluxed overnight, cooled, diluted with ether and washed with saturated aqueous ammonium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ether 90/10 to 80/20) to provide the title compound 18 (1 g, 47 %), Rf = 0.3 (silica gel, hexanes/ethyl acetate 90/10).

Example 15 Preparation of compound of formula 18

2,3-*O*-(Methylethylidene)-4-*C*-spirocyclopropyl-D-erythrofuranose

A mixture of methyl 2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-D-erythrofuranoside (2.57 g, 12.8 mmol), 1N aqueous hydrochloric acid (20 mL) and tetrahydrofuran (20 mL) was refluxed for 1 hour. The cooled reaction mixture was neutralized with DOWEX® 1X8-200 ion exchange resin (OH form), filtered and rinsed with methanol. The combined filtrates were concentrated under reduced pressure and azeotroped twice with dimethylformamide. The residue was dissolved in dimethylformamide (10 mL). *p*-Toluenesulfonic acid monohydrate (catalytic) and 2,2-dimethoxypropane (4.6 mL, 32 mmol) were added. After stirring 4 hours at room temperature, the reaction mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ether 70/30 to 40/60). Yield: 1.2 g, 50 %, Rf = 0.4 (silica gel, hexanes/ethyl acetate 60/40).

Example 16 Preparation of compound of formula 4

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in example 12. Thus coupling of 2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-D-erythrofuranose (450 mg, 2.42 mmol) with 4-*N*-(4-fluorophenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (**20**, 1.47 g, 4.84 mmol) provided the title nucleoside (294 mg, 26 %), Rf = 0.6 (silica gel, hexanes/ethyl acetate 70/30).

Example 17 Preparation of compound of formula 1

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine; Table 4 #150

The title compound was synthesized following a procedure analogous to the synthesis described in Example 13. Thus 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine (289 mg, 0.6 mmol) provided the titled deprotected nucleoside (159 mg, 60 %), Rf = 0.5 (silica gel, dichloromethane/methanol 90/10), m.p. 142° C.

Example 18 Preparation of compound of formula 4

4-Chloro-5-iodo-7-(5-deoxy-4-*C*-methyl-2,3-*O*-(methylethylidene)-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 12. Thus coupling of 5-deoxy-4-*C*-methyl-2,3-*O*-(methylethylidene)-D-ribofuranose (550 mg, 2.9 mmol) with 4-chloro-5-iodo-pyrrolo[2,3-*d*]pyrimidine (1.23 g, 4.35 mmol) provided the titled nucleoside (581 mg, 44 %), Rf = 0.4 (silica gel, hexanes/ethyl acetate 60/40).

Example 19 Preparation of compound of formula 1

4-Chloro-5-iodo-7-(5-deoxy-4-*C*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 13. Thus 4-chloro-5-iodo-7-(5-deoxy-4-*C*-methyl-2,3-*O*-(methylethylidene)-β-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine (100 mg, 0.22 mmol) provided the titled deprotected nucleoside (14 mg, 15 %), Rf = 0.45 (silica gel, dichloromethane/methanol 90/10), m.p. 173-174°C.

Example 20 Preparation of compound of formula 4

4-Chloro-5-iodo-7-(2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 12. Thus coupling of 2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-D-erythrofuranose (500 mg, 2.66 mmol) with 4-chloro-5-iodo-pyrrolo[2,3-*d*]pyrimidine (1.11 g, 3.99 mmol) provided the titled nucleoside (402 mg, 34 %), Rf = 0.7 (silica gel, hexanes/ethyl acetate 70/30).

Example 21 Preparation of compound of formula 1

4-Amino-5-iodo-7-(4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine; Table 4 #175

Liquid ammonia (15 mL) was added to a solution of 4-chloro-5-iodo-7-(2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine (200 mg, 0.45 mmol) in methanol (15 mL) at -78°C. The reaction mixture was heated at 100°C in a sealed steel bomb for 24 hours. Ammonia was slowly released from the cooled bomb and the resulting solution was concentrated under reduced pressure. The residue was disolved in 70 % aqueous trifluoroacetic acid and stirred at room temperature. After 30 minutes the reaction mixture was concentrated under reduced pressure and azeotroped twice with water and twice with ethanol. The residue was neutralized with saturated aqueous sodium bicarbonate and the precipitated nucleoside was filtered and rinsed with water. The solid was recovered and recrystallized from ethanol. Yield: 73 mg, 42 %, Rf = 0.35 (silica gel, dichloromethane/methanol 90/10), m.p. 232°C (dec).

Example 22 Preparation of compound of formula 12
4-C-Methyl-2,3,5-tri-O-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*lyxo*-pentane

The title compound was synthesized following a procedure analogous to the synthesis described in Example 9. Thus the compound of Example 2 (5 g, 9.8 mmol) gave the title compound (3.94 g, 84 %) from a separable 12/1 epimeric mixture, Rf = 0.38 (silica gel, hexanes/ethyl acetate 70/30).

Example 23 Preparation of compound of formula 2
4-C-Methyl-2,3,5-tri-O-(phenylmethyl)-D-lyxofuranose

The title compound was synthesized following a procedure analogous to the synthesis described in Example 4. Thus the compound of Example 22 (3.94 g, 7.51 mmol) gave the title compound (2.6 g, 80 %), Rf = 0.25 (silica gel, hexanes/ethyl acetate 70/30).

Example 24 Preparation of compound of formula 4
4-N-[4-(Dimethylaminomethyl)phenyl]amino-5-phenyl-7-(4-C-methyl-2,3,5-tri-O-(phenylmethyl)-β-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 12. Thus coupling of 4-C-methyl-2,3,5-tri-O-(phenylmethyl)-D-lyxofuranose (500 mg, 1.15 mmol) with 4-N-[4-(dimethylaminomethyl)phenyl]amino-5-phenyl-pyrrolo[2,3-d]pyrimidine (593 mg, 1.5 mmol) provided an unseparable mixture of the title compound and its N1-isomer and tris[2-(2-methoxyethoxy)ethyl]amine (836 mg); Rf = 0.6 (silica gel, dichloromethane/methanol 90/10).

Example 25 Preparation of formula 1

4-*N*-[4-(Dimethylaminomethyl)phenyl]amino-5-phenyl-7-(4-*C*-methyl-β-D-lyxofuranosyl)pyrrolo[2,3-*d*]-pyrimidine; Table 2 # 64

An orange solution of palladium chloride (400 mg) in anhydrous methanol (10 mL) was degassed and stirred under hydrogen (1 atm) for 10 minutes. A solution of 4-*N*-[4-(dimethylaminomethyl)phenyl]amino-5-phenyl-7-(4-*C*-methyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-lyxofuranosyl)-pyrrolo[2,3-*d*]pyrimidine, its N1-isomer and tris[2-(2-methoxyethoxy)ethyl]amine (786 mg) in solution in anhydrous methanol (10mL) was added to the suspension of reduced palladium. The heterogeneous reaction mixture was stirred at room temperature under hydrogen (1 atm) for 6 hours, filtered through Celite® and the filtering pad was rinsed with boiling methanol. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in 0.1N hydrochloric acid and washed twice with ethyl acetate. The pH of the aqueous solution was brought to 12 with 1N aqueous sodium hydroxide and the resulting solution was extracted 3 times with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/30 % aqueous ammonium hydroxide 90/10/1 to 80/20/1). The partially purified nucleoside was further purified by HPLC (C18, 50X250 mm, methanol/(water/methanol/acetic acid 95/5/0.5) 45/55, 16.5 mL/minute, λ_{max}= 299 nm, Rt= 20.6 minutes) and crystallized from ethanol. Yield: 26.8 mg, Rf = 0.25 (silica gel, dichloromethane/methanol 80/20), m.p. 205-206° C.

Example 26 Preparation of compound of formula 12

4-*C*-Methyl-2,3,5-tri-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

A solution of the compound of Example 8 (4 g, 10 mmol) in dry tetrahydrofuran (100 mL) was added dropwise over 10 minutes to a solution of [(phenylmethyl)oxy]methyllithium (1.8 mmol) (Still, W. C. *J. Am. Chem. Soc. 100*, 1481 (1978)) in dry tetrahydrofuran (50 mL) at -78° C. After stirring for 10 minutes at -78° C, the reaction mixture was quenched by slow addition of a solution of acetic acid (2.3 mL) in dry tetrahydrofuran (50 mL) over 5 minutes at -78° C. The quenched

solution was warmed to room temperature, diluted with ethyl acetate and washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 90/10 to 75/25). Yield: 3.68 g, 70 %, Rf = 0.45 (silica gel, hexanes/ethyl acetate 70/30).

Example 27 Preparation of compound of formula 2
4-C-Methyl-2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranose

The title compound was synthesized following a procedure analogous to the synthesis described in Example 4. Thus the compound of Example 26 (3.68 g, 7 mmol) gave 2.22 g, 73 %, Rf = 0.25 (silica gel, hexanes/ethyl acetate 70/30).

Example 28 Preparation of compound of formula 4
4-*N*-Phenylamino-5-phenyl-7-(4-*C*-methyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 12. Thus coupling of 4-*C*-methyl-2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranose (500 mg, 1.15 mmol) with 4-*N*-phenylamino-5-phenyl-pyrrolo[2,3-*d*]pyrimidine (494 mg, 1.73 mmol) provided the titled nucleoside (165 mg, 20 %); Rf = 0.6 (silica gel, hexanes/ethyl acetate 70/30).

Example 29 Preparation of compound of formula 1
4-*N*-Phenylamino-5-phenyl-7-(4-*C*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine; Table 2 #81

The title compound was synthesized following a procedure analogous to the synthesis described in Example 24. Thus 4-*N*-phenylamino-5-phenyl-7-(4-*C*-methyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine (144 mg) provided the titled deprotected nucleoside (63 mg, 73 %), Rf = 0.45 (silica gel, dichloromethane/methanol 90/10), m.p. 211-213° C.

Example 30 Preparation of compound of formula 4

4-*N*-[4-(Dimethylaminomethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 12. Thus coupling of 2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-D-erythrofuranose (350 mg, 1.88 mmol) with 4-*N*-[4-(dimethylaminomethyl)phenyl]amino-5-phenyl-pyrrolo[2,3-*d*]pyrimidine (1.11 g, 3.99 mmol) provided an unseparable mixture of the titled nucleoside, its N1-isomer and tris[2-(2-methoxyethoxy)ethyl]amine (1.31 g); Rf = 0.45 (silica gel, dichloromethane/methanol 90/10).

Example 31 Preparation of compound of formula 1

4-*N*-[4-(Dimethylaminomethyl)phenyl]amino-5-phenyl-7-(4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo-[2,3-*d*]pyrimidine; Table 4 #158

A mixture of 4-*N*-[4-(dimethylaminomethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-4-*C*-spirocyclopropyl-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine, its N1-isomer and tris[2-(2-methoxyethoxy)ethyl]amine (1.31 g) was dissolved in methanol (10 mL) and 0.1N hydrochloric acid (10 mL). The pH was adjusted to pH=1.5 with 6N hydrochloric acid (0.5 mL) and the homogeneous solution was refluxed for one hour. The reaction mixture was diluted with 0.1 N hydrochloric acid and washed twice with ethyl acetate. The pH of the aqueous solution was brought to 12 with 1N aqueous sodium hydroxide and the resulting solution was extracted 3 times with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/30 % aqueous ammonium hydroxide 90/10/1 to 80/20/1). The partially purified nucleoside was further purified by HPLC (C18, 50X250 mm, methanol/(water/methanol/acetic acid 95/5/0.5) 45/55, 18 mL/minute, λ_{max}= 299 nm, Rt= 17 minutes) and crystallized from ethyl acetate to provide the title compound (Rf = 0.25 (silica gel, dichloromethane/methanol 80/20). MS, calculated (M+H) = 472.23; found = 472.

Example 32 Preparation of compound of formula 4
4-*N*-Phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine

Oxalyl chloride (.55 mL, 6.3 mmol) was added dropwise, keeping the temperature below 35° C, to a solution of *N,N*-dimethylformamide (4.8 mL, 63 mmol) in toluene (5.4 mL) and acetonitrile (1.9 mL). The slushy mixture was stirred at room temperature for 15 minutes then cooled to -12° C. A solution of 2,3-*O*-(methylethylidene)-β-D-erythrofuranose (1 g, 6.24 mmol)(Cohen, N. *et al. J. Am. Chem. Soc.* 105, 3661 (1983)) in toluene (1.2 mL) was added to the reaction mixture maintaing the temperature below -12° C. After stirring at -12° C for 20 minutes the solution was cooled to -16° C and a solution of triethylamine (1.1 mL, 7.9 mmol) in toluene (1 mL) was added maintening the temperature below 0° C. The precipitate was stirred 15 minutes at 0° C, filtered off over a pad of Celite® and rinsed with toluene. The combined filtrates were added to a mixture of 4-*N*-phenylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (2.85 g, 1 mmol), finely powdered potassium hydroxide (85%, 1.31 g, 2 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (4 mL, 1.25 mmol) in dry toluene which had been stirring at room temperature for 2 hours. After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 70/30 to 50/50). Yield: 969 mg, 36 %, Rf = 0.55 (silica gel, hexanes/ethyl acetate 60/40).

Example 33 Preparation of compound of formula 1
4-*N*-Phenylamino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine; Table 1 #27

The title compound was synthesized following a procedure analogous to the synthesis described in Example 13. Thus 4-*N*-phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-*d*]pyrimidine (969 mg, 2.26 mmol) provided the title nucleoside (401 mg, 46 %), Rf = 0.5 (silica gel, dichloromethane/methanol 90/10), m.p. 210.5-211.5° C.

Example 34 Preparation of compound of formula 12
4-*C*-[(Methoxy)methyl]-2,3,5-tri-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*lyxo*-pentane

A solution of the compound of Example 2 (1.02 g, 2 mmol) in dry tetrahydrofuran (40 mL) was added dropwise over 5 minutes to a solution of [(methyl)oxy]methyllithium (6 mmol) (Still, W. C. *J. Am. Chem. Soc.* 1978, *100*, 1481) in dry tetrahydrofuran (40 mL) at -78° C. After stirring for 20 minutes at -78° C, the reaction mixture was quenched with saturated aqueous ammonium chloride, warmed to room temperature, diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 90/10 to 75/25). Yield: 0.48 g, 43 %, Rf = 0.45 (silica gel, hexanes/ethyl acetate 70/30).

Example 35 Preparation of compound of formula 2
4-*C*-Methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-D-lyxofuranose

The title compound was synthesized following a procedure analogous to the synthesis described in Example 4. Thus the compound of Example 34 (3.53 g, 6.3 mmol) gave the title compound (1 g, 34 %), Rf = 0.25 (silica gel, hexanes/ethyl acetate 70/30).

Example 36 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-lyxofuranosyl)pyrrolo[2,3-*d*]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 12. Thus coupling of 4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-D-lyxofuranose (500 mg, 1.08 mmol) with 4-*N*-(4-fluorophenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (0.5 g, 1.64 mmol) provided the title compound (328 mg, 40 %); Rf = 0.6 (silica gel, hexanes/ethyl acetate 70/30).

Example 37 Preparation of compound of formula 1
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-β-D-lyxofuranosyl)pyrrolo[2,3-*d*]pyrimidine: Table 3 #372

The title compound was synthesized following a procedure analogous to the synthesis described in Example 25. Thus 4-*N*-(Fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-lyxofuranosyl)pyrrolo-[2,3-*d*]pyrimidine (430 mg) provided the titled deprotected nucleoside Rf = 0.5 (silica gel, dichloromethane/methanol 90/10). MS, calculated (M+H)= 481; found = 481. m.p. 205-206 °C.

Example 38 Preparation of Compound of formula 4
1-(2,3-Di-O-acetyl-β-D-erythrofuranosyl)-3-(4-chlorophenyl)-4-*N*-phenylaminopyrazolo[3,4-d]pyrimidine

A mixture of 1,2,3-tri-*O*-acetyl-D-erythrofuranose (619 mg, 2.5 mmol) obtained according to Kline, *J.Org.Chem.* 57:6, 1772 (**1992**), 3-(4-chlorophenyl)-4-*N*-phenylaminopyrazolo[3,4-d]pyrimidine (809 mg, 2.51 mmol.) obtained according to the methods in U.S. application Serial No. 08/014,190, and boron trifluoride diethyl etherate (620 μL, 5 mmol) in nitromethane (20 mL) was refluxed for 1 hour. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexanes/ethyl acetate 80/20 to 50/50) to provide the protected nucleoside (625 mg, 49%), Rf=0.2 (silica, hexanes/ethyl acetate 70/30).

Example 39 Preparation of compound of formula 1 3-(4-Chlorophenyl)-1-(β-D-erythrofuranosyl)-4-*N*-phenylaminopyrazolo[3,4-d]pyrimidine: Table 5 #432

A 0.5 M solution of sodium methoxide in methanol (2.4 mL, 1.2mmol) was added to a solution of 1-(2,3-di-*O*-acetyl-β-D-erythrofuranosyl)-3-(4-chlorophenyl)-4-*N*-phenylaminopyrazolo[3,4-d]pyrimidine (308 mg, 0.6 mmol) in methanol (10 mL) at 0 °C. After stirring at 0 °C for 30 minutes, the reaction mixture was quenched with acetic acid (0.25 mL) and concentrated under reduced pressure. The residue was purified by chromatography (silica, dichloromethane/methanol 96/4 to 90/10). Recrystallization from ethanol afforded the pure product. Rf=0.6, (silica, dichloromethane/methanol 90:10), m.p. 194-195° C.

Example 40 Preparation of compound of formula 4 4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 32. Thus coupling of 2,3-*O*-(methylethylidene)-β -D-erythrofuranose (5.6 g, 35 mmol) with 4-*N*-(4-fluorophenyl)amino-5-phenylpyrrolo[2,3-d]pyrimidine (15.9 g, 52.5 mmol) provided the title nucleoside (4.58 g, 29 %); Rf = 0.5 (silica gel, hexanes/ethyl acetate 80/20).

Example 41 Preparation of compound of formula 1 4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine: Table 1 #28

A solution of 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (3.26 g) in 70 % aqueous trifluoroacetic acid (30 mL) was stirred at rt for 1 hour. The reaction mixture was concentrated under reduced pressure and azeotroped twice with water and twice with ethanol. The residue was purified by chromatography (silica, dichloromethane/methanol 95/5 to 90/10). Recrystallization from ethanol afforded the pure product (2.35 g, 79 %); Rf = 0.5 (silica, dichloromethane/methanol 90/10), m.p. 194-195°C.

Example 42 Preparation of compound of formula 4

4-*N*-(4-Fluorophenyl)amino-5-(4-fluorophenyl)-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 32. Thus coupling of 2,3-*O*-(methylethylidene)-β-D-erythrofuranose (1 g, 6.2 mmol) with 4-*N*-(4-fluorophenyl)amino-5-(4-fluorophenyl)pyrrolo[2,3-d]pyrimidine (3 g, 9.3 mmol) provided the title nucleoside (580 mg, 20 %); Rf = 0.6 (silica gel, hexanes/ethyl acetate 70/30).

Example 43 Preparation of compound of formula 1

4-*N*-(4-Fluorophenyl)amino-5-(4-fluorophenyl)-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine ; Table 1 #29

The title compound was synthesized following a procedure analogous to the synthesis described in Example 41. Thus 4-*N*-(4-fluorophenyl)amino-5-(4-fluorophenyl)-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (580 mg) provided the title compound (244 mg, 41 %); Rf = 0.7 (silica gel, dichloromethane/methanol 80/20), m.p. 200-202° C.

Example 44 Preparation of compound of formula 4

4-*N*-(4-Chlorophenyl)amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 32. Thus coupling of 2,3-*O*-(methylethylidene)-β-D-erythrofuranose (900 mg, 5.6 mmol) with 4-*N*-(4-chlorophenyl)amino-5-phenylpyrrolo[2,3-d]pyrimidine (900 mg, 2.8 mmol) provided the title nucleoside (744 mg, 57 %); Rf = 0.7 (silica gel, hexanes/ethyl acetate 70/30).

Example 45 Preparation of compound of formula 1
4-*N*-(4-Chlorophenyl)amino-5-phenyl-7-(β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine; Table 1 #299

The title compound was synthesized following a procedure analogous to the synthesis described in Example 41. Thus 4-*N*-(4-chlorophenyl)amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (744 mg) provided the title compound (500 mg, 74 %); Rf = 0.5 (silica gel, dichloromethane/methanol 90/10), m.p. 212-213° C.

Example 46 Preparation of compound of formula 4
4-Chloro-5-iodo-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 32. Thus coupling of 2,3-*O*-(methylethylidene)-β -D-erythrofuranose (3.8 g, 21.8 mmol) with 4-chloro-5-iodopyrrolo[2,3-d]pyrimidine (Pudlo, J. S. *J. Med. Cem.* **1990**, *33*, 1984, 2.54 g, 10.9 mmol) provided the title nucleoside (2.64 g, 62 %); Rf = 0.7 (silica gel, hexanes/ethyl acetate 70/30).

Example 47 Preparation of compound of formula 1
4-Amino-5-iodo-7-(-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine; Table 1 #300

The title compound was synthesized following a procedure analogous to the synthesis described in Example 21. Thus 4-chloro-5-iodo-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (714 mg) gave after chromatography (silica gel, dichloromethane/methanol 95/5 to 85/15) and crystallization from ethanol the title nucleoside (270 mg, 40 %), m.p. 258° C (dec).

Example 48 Preparation of compound of formula 4
4-*N*-[4-(2-((1,1-Dimethylethyl)dimethylsilyloxy)ethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 32. Thus coupling of 2,3-*O*-(methylethylidene)-β -D-erythrofuranose (1 g, 6.2 mmol) with 4-*N*-[4-(2-((1,1-dimethylethyl)dimethylsilyloxy)ethyl)phenyl]amino-5-phenylpyrrolo[2,3-d]pyrimidine (1 g, 2.2 mmol) provided the title nucleoside (551 mg, 42 %); Rf = 0.7 (silica gel, hexanes/ethyl acetate 70/30).

Example 49 Preparation of compound of formula 4
4-*N*-[4-(2-hydroxyethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

A mixture of tetraethylammonium fluoride hydrate (0.86 g, 5.76 mmol) and 4-*N*-[4-(2-((1,1-dimethylethyl)dimethylsilyloxy)ethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (2.7 g, 4.6 mmol) in dimethylformamide (55 mL) was stirred at rt for 18 hours. The reaction mixture was concentrated under reduced pressure, diluted in ethyl acetate and washed with saturated aqueous ammonium chloride. The aqueous layer was back extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, hexanes/ethyl acetate 90/10 to 70/30) to give the title compound (2.12 g, 98 %); Rf = 0.2 (silica gel, hexanes/ethyl acetate 70/30).

Example 50 Preparation of compound of formula 4
4-*N*-[4-(2-(4-Morpholino)ethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

A mixture of 4-*N*-[4-(2-hydroxyethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (158 mg, 3.34 mmol) and methyl triphenoxyphosphonium iodide (460 mg, 1 mmol) in dichloromethane (6 mL) was stirred overnight at rt. The reaction mixture was quenched with methanol (1 mL) and poured into a 0.5 M solution of sodium

thiosulfate and extracted with ethyl acetate. The combined organic extracts were washed with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was dissolved in dioxane (30 mL) and morpholine was added (0.84 mL, 9.6 mmol). The resulting solution was refluxed for 24 hours. After cooling to rt, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, dichloromethane/methanol 95/5) to give the title compound, Rf = 0.7 (silica gel, dichloromethane/methanol 90/10).

<u>Example 51</u> <u>Preparation of compound of formula 1</u>
<u>4-*N*-[4-(2-(4-Morpholino)ethyl)phenyl]amino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine; Table 1 #301</u>

The title compound was synthesized following a procedure analogous to the synthesis described in Example 41. Thus 4-*N*-[4-(2-(4-morpholino)ethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (1.7 g) provided the title compound (150 mg, 10 %) after recrystallization from methanol/water; Rf = 0.1 (silica gel, dichloromethane/methanol 90/10), m.p. 128-130°C.

<u>Example 52</u> <u>Preparation of compound of formula 4</u>
<u>4-*N*-[4-(2-(1-(4-*tert*-Butyloxycarbonylpiperazino))ethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine</u>

The title compound was synthesized following a procedure analogous to the synthesis described in Example 50. Thus 4-*N*-[4-(2-hydroxyethyl)phenyl]amino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (701 mg, 1.48 mmol) and substituting *tert*-butyl 1-piperazinecarboxylate (830 mg, 4.46 mmol) for morpholine provided the title compound; Rf = 0.45 (C18, methanol/0.1 N hydrochloric acid 50/50).

Example 53 Preparation of compound of formula 1
4-*N*-[4-(2-(1-Piperazino)ethyl)phenyl]amino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine trihydrochloride salt : Table 1 #43

A solution of 4-*N*-[4-(2-(1-(4-*tert*-butyloxycarbonylpiperazino))ethyl)phenyl]amino-5-phenyl-7-(2,3-O-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (931 mg) in 70 % aqueous trifluoroacetic acid (65 mL) was stirred at 0C for 1 hour and at rt for 1 hour. The reaction mixture was concentrated under reduced pressure and azeotroped twice with water and twice with ethanol. The residue was purified by HPLC (C18, 50X250 mm, methanol/(0.1 % aqueous trifluoroacetic acid 50/50, 15 mL/minute, λ_{max}= 260 nm, Rt= 15.7 minutes) and lyophilized to give the title compound (339 mg, 37 %); Rf = 0.75 (C18, methanol/0.1 N hydrochloric acid 50/50), m.p. 150-180°C (dec).

Example 54 Preparation of compound of formula 9
Methyl 5-*O*-methyl-2,3-di-*O*-(phenylmethyl)-D-ribofuranoside

A solution of methyl 5-*O*-methyl-D-ribofuranoside (Dubois L. et al. *Tetrahedron* **1993**, *49*(4), 901-910, 2 g, 11.2 mmol) in dimethylformamide (10 mL) was added dropwise to a suspension of sodium hydride (60 % in oil, 2.25 g, 563 mmol) in dimethylformamide (54 mL). After stirring at rt for 45 minutes, a solution of benzyl bromide (4 mL, 33.6 mmol) was added dropwise in dimethylformamide (4 mL). The reaction mixture was stirred at rt overnight, quenched with methanol and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexanes/ethyl acetate 70/30 to 50/50) to provide the α anomer (2.86 g, 71 %) and the β anomer (0.86 g, 21 %); α anomer Rf = 0.5, β anomer Rf = 0.4 (silica, hexanes/ethyl acetate 50/50).

Example 55 Preparation of compound of formula 10

5-*O*-Methyl-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

The title compound was synthesized following a procedure analogous to the synthesis described in example 1. Thus methyl 5-*O*-methyl-2,3-di-*O*-(phenylmethyl)-D-ribofuranoside (3.72 g, 10.4 mmol) gave the title compound (3.74 g, 83 %), Rf = 0.45 (silica, hexanes/ethyl acetate 50/50).

Example 56 Preparation of compound of formula 11

(3S, 4R)-1-Methoxy-3,4-di-[(phenylmethyl)oxy]-5-(1,3-dithian-2-yl)pentan-2-one

The title compound was synthesized following a procedure analogous to the synthesis described in example 2. Thus 5-*O*-methyl-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane (3.74 g, 8.61 mmol) gave the title compound (3.32 g, 89 %), Rf = 0.3 (silica, hexanes/ethyl acetate 70/30).

Example 57 Preparation of compound of formula 12

4-*C*-Methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

The title compound was synthesized following a procedure analogous to the synthesis described in example 3. Thus (3S, 4R)-1-methoxy-3,4-di-[(phenylmethyl)oxy]-5-(1,3-dithian-2-yl)pentan-2-one (3.32 g, 7.67 mmol) gave the title compound (1.47 g, 34 %); Rf = 0.45 (silica, hexanes/ethyl acetate 70/30).

Example 58 Preparation of compound of formula 2

4-*C*-Methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranose

The title compound was synthesized following a procedure analogous to the synthesis described in example 4. Thus 4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane (1.47 g, 2.65 mmol) gave the title compound (0.91 g, 74 %); Rf = 0.2 (silica, hexanes/ethyl acetate 70/30).

Example 59 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in example 12. Thus coupling of 4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-D-ribofuranose (500 mg, 1.08 mmol) with 4-*N*-(fluorophenyl)amino-5-phenyl-pyrrolo[2,3-*d*]pyrimidine (0.5 g, 1.64 mmol) provided the title nucleoside (328 mg, 40 %); Rf = 0.5 (silica, hexanes/ethyl acetate 70/30).

Example 60 Preparation of compound of formula 1
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine; Table 3 #352

The title compound was synthesized following a procedure analogous to the synthesis described in example 25. Thus 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-2,3,5-tri-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (0.69 g, 0.92 mmol)) provided the deprotected nucleoside (134 mg, 30 %), Rf = 0.4 (silica, dichloromethane/methanol 90/10), m.p. 198-199° C.

Example 61 Preparation of compound of formula 9
Methyl 5-azido-5-deoxy-D-ribofuranoside

A solution of methyl 5-azido-5-deoxy-2,3-O-(methylethylidene)-D-ribofuranoside (Browne et al., U.S. Patent Serial No. 08/812,916, 15.3 g, 70.3 mmol) and *para*-toluenesulfonic acid monohydrate (0.69 g, 3.6 mmol) in methanol (750 mL) was refluxed for 18 hours. The reaction mixture was quenched with pyridine (8.4 mL, 10 mmol), concentrated under reduced pressure and purified by flash chromatography (silica, hexanes/ethyl acetate 50/50 to 30/70) to provide the title compound (8.19 g, 62 %); Rf = 0.15 (silica, hexanes/ethyl acetate 70/30).

Example 62 Preparation of compound of formula 9

Methyl 5-azido-5-deoxy-2,3-di-*O*-(phenylmethyl)-D-ribofuranoside

The title compound was synthesized following a procedure analogous to the synthesis described in example 54. Thus methyl 5-azido-5-deoxy-D-ribofuranoside (8.19 g, 43.3 mmol) gave the title compound as a mixture of α anomer (2.2 g, 14 %) and the β anomer (12.46 g, 78 %); β anomer Rf = 0.6, α anomer Rf = 0.4 (silica, hexanes/ethyl acetate 70/30).

Example 63 Preparation of compound of formula 10

5-Azido-5-deoxy-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

The title compound was synthesized following a procedure analogous to the synthesis described in example 1. Thus methyl 5-azido-5-deoxy-2,3-di-*O*-(phenylmethyl)-D-ribofuranoside (12.45 g, 33.7 mmol) gave the title compound (13.48 g, 90 %), Rf = 0.45 (silica, hexanes/ethyl acetate 70/30).

Example 64 Preparation of compound of formula 11

(3S, 4R)-1-Azido-3,4-di-[(phenylmethyl)oxy]-5-(1,3-dithian-2-yl)pentan-2-one

The title compound was synthesized following a procedure analogous to the synthesis described in example 2. Thus 5-Azido-5-deoxy-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane (13.48 g, 31 mmol) gave the title compound (9.91 g, 74 %), Rf = 0.5 (silica, hexanes/ethyl acetate 70/30).

Example 65 Preparation of compound of formula 12

4-*C*-Azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane

The title compound was synthesized following a procedure analogous to the synthesis described in example 3. Thus reaction of [((4-methoxyphenyl)methyl)oxy]methyllithium (prepared using a procedure analogous to the one described by Still, W. C. *J. Am. Cem. Soc.* **1978**, 100,1481 for the

preparation of [(phenylmethyl)oxy]methyllithium, 7.78 g, 18.2 mmol) and (3S, 4R)-1-azido-3,4-di-[(phenylmethyl)oxy]-5-(1,3-dithian-2-yl)pentan-2-one (4.02 g, 9.06 mmol) gave the title compound (2.07 g, 39 %); Rf = 0.45 (silica, hexanes/ethyl acetate 70/30).

Example 66 Preparation of compound of formula 2
4-*C*-Azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-D-ribofuranose

The title compound was synthesized following a procedure analogous to the synthesis described in example 4. Thus 4-*C*-azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3,-di-*O*-(phenylmethyl)-1-(1,3-dithian-2-yl)-D-*ribo*-pentane (2.07 g, 3.47 mmol) gave the title compound (1.19 g, 68 %); Rf = 0.4 (silica, hexanes/ethyl acetate 70/30).

Example 67 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in example 12. Thus coupling of 4-*C*-azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-D-ribofuranose (1.19 mg, 2.3 mmol) with 4-*N*-(fluorophenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (2.17 g, 7.1 mmol) provided the title nucleoside (656 mg, 35 %); Rf = 0.6 (silica, hexanes/ethyl acetate 70/30).

Example 68 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-aminomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

A mixture 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (448 mg, 0.57 mmol) and triphenylphosphine (300 mg, 0.11 mmol) in

toluene (30 mL) was refluxed for 2 hours. The reaction mixture was quenched with methanol and reflux was carried on for 30 minutes. After cooling, the solution was concentated under reduced pressure and purified by flash chromatography (silica, dichloromethane/methanol 95/5) to provide the title compound (284 mg, 65 %), Rf = 0.4 (silica, dichloromethane/methanol 90/10).

Example 69 Preparation of compound of formula 1
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-aminomethyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine dihydrochloride: Table 3 #392

Iodotrimethylsilane (0.4 mL, 28 mmol) was added dropwise to a solution of 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(4-*C*-aminomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-β -D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (166 mg, 0.22 mmol) in chloroform (10 mL) at 0° C. After stirring at 0° C for 40 minutes and rt for 24 hours, the reaction mixture was quenched with methanol and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, dichloromethane/methanol/28% aqueous ammonium hydroxide 80/20/1). HPLC (C18, 50X250 mm, methanol/0.1 % aqueous trifluoroacetic acid 65/35, 15 mL/minute, λ_{max}= 260 nm, Rt= 21.64 minutes) and lyophilization with 1 N hydrochloric acid gave the title compound (64 mg, 32 %); m.p. 200-220 °C (dec).

Example 70 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (122 mg, 0.53 mmol) was added to a solution of 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-5-*O*-[(4-methoxyphenyl)methyl]-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (212 mg, 0.27 mmol) in dichloromethane/water (2/1, 7.5 mL). After stirring at rt overnight, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride.

The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexanes/ethyl acetate 70/30) to give the title compound (51 mg, 28 %); Rf = 0.35 (silica, hexanes/ethyl acetate 70/30).

Example 71 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-5-*O*-[(4-methylphenyl)sulfonyl]-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

para-Toluenesulfonyl chloride (76 mg, 0.4 mmol) was added to a solution of 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (51 mg, 0.08 mmol), pyridine (0.062 mL, 0.8 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) in dichloromethane at 0° C. After stirring at 0° C for 30 minutes, at rt for 3 days and being refluxed for 2 hours, more *para*-toluenesulfonyl chloride, pyridine and 4-dimethylaminopyridine was added and the reaction mixture was stirred at rt for 2 days. Concentration under reduced pressure and purification by flash chromatography (silica, hexanes/ethyl acetate 95/5 to 80/20) gave the title compound (51 mg, 50 %); Rf = 0.5 (silica, hexanes/ethyl acetate 70/30).

Example 72 Preparation of compound of formula 4
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-spiro(3-azetidino)-2,3-di-*O*-(phenylmethyl)-β -D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

A mixture of 4-*N*-(4-fluorophenyl)amino-5-phenyl-7-(4-*C*-azidomethyl-5-*O*-[(4-methylphenyl)sulfonyl]-2,3-di-*O*-(phenylmethyl)-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (31 mg, 0.038 mmol) and triphenylphosphine was refluxed for 15 minutes, cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, dichloromethane/methanol) to give the title compound (22 mg, 94 %); Rf = 0.6 (silica, dichloromethane/methanol/1 % aqueous ammonium hydroxide 80/20/1).

Example 73 Preparation of compound of formula 1
4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-spiro(3-azetidino)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine; Table 4a #414

The title compound was synthesized following a procedure analogous to the synthesis described in example 69. Thus 4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-spiro(3-azetidino)-2,3-di-*O*-(phenylmethyl)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (4.8 mg) gave the title compound; Rf=0.15 (silica, dichloromethane/methanol 80/20); MS, calculated (M+H) = 448.16; found = 448.

Example 74 Preparation of compound of formula 4
4-*N*-[(1,1,2-Trimethylpropyl)dimethylsilyloxymethyl]phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 32. Thus coupling of 2,3-*O*-(methylethylidene)-β-D-erythrofuranose (3.6 g, 22.6 mmol) with 4-*N*-[(1,1,2-trimethylpropyl)dimethylsilyloxymethyl]phenylamino-5-phenylpyrrolo[2,3-d]pyrimidine (5 g, 11.3 mmol) provided the title nucleoside (4.21 g, 64 %); Rf = 0.65 (silica, hexanes/ethyl acetate 70/30).

Example 75 Preparation of compound of formula 4
4-*N*-(Hydroxymethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

Triethylammonium fluoride hydrate (36 mg, 0.24 mmol) was added to a solution of 4-*N*-[(1,1,2-trimethylpropyl)dimethylsilyloxymethyl]phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (101 mg, 0.17 mmol) in dimethylformamide (2 mL) at rt. After stirring at rt for 30 minutes, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexanes/ethyl acetate 70/30 to 50/50) to provide the title compound (68 mg, 88 %); Rf = 0.2 (silica, hexanes/ethyl acetate 70/30).

Example 76 Preparation of compound of formula 4
4-*N*-(Diethylaminomethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

Triphenoxyphosphonium iodide (1 g, 2.2 mmol) was added to a solution of 4-*N*-(hydroxymethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (500 mg, 1.09 mmol) in dichloromethane (4 mL) at rt. After stirring at rt for 30 minutes, diethylamine (0.46 mL, 4.5 mmol) was added and stirring was carried on at rt overnight. The reaction mixture was then diluted with ethyl acetate and washed with 0.5 N aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexanes/ethyl acetate 75/25 to 25/75) to provide the title compound (469 mg, 84 %); Rf = 0.1 (silica, hexanes/ethyl acetate 70/30).

Example 77 Preparation of compound of formula 1
4-*N*-(Diethylaminomethyl)phenylamino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine dihydrochloride salt: Table 1 #303

4-*N*-(Diethylaminomethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (2 mmol) was dissolved in 70% aqueous trifluoroacetic acid and stirred at rt for 2 hours. The volatiles were evaporated and the residue was coevaporated with water (2X20 mL) and ethanol (2X20 mL). The residue was purified by HPLC (C18, 50X250 mm, methanol/(water/0.1% trifluoroacetic acid) 50/50), 15 mL/minute, λ_{max}= 260 nm, Rt= 23.4 minutes) and lyophilized three times with 0.5 N hydrochloric acid to afford the pure product Rf = 0.3 (silica, dichloromethane/methanol/28% aqueous ammonium hydroxide 80/20/1); m.p. 80-140° C (dec).

Example 78 Preparation of compound of formula 4
4-*N*-[1-(4-*tert*-Butyloxycarbonylpiperazino)methyl]phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

The title compound was synthesized following a procedure analogous to the synthesis described in Example 76. Thus 4-*N*-(hydroxymethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (100 mg, 0.22 mmol) and *tert*-butyl 1-piperazinecarboxylate (160 mg, 0.86 mmol) gave the title compound (109 mg, 79 %); Rf = 0.35 (silica, hexanes/ethyl acetate 50/50).

Example 79 Preparation of compound of formula 1
4-*N*-(1-Piperazinomethyl)phenylamino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine dihydrochloride salt: Table 1 #304

The title compound was synthesized following a procedure analogous to the synthesis described in Example 77. Thus 4-*N*-[1-(4-*tert*-butyloxycarbonylpiperazino)methyl]phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine gave the title compound; MS, calculated (M+H) = 486.58, found = 487.

Example 80 Preparation of compound of formula 4
4-*N*-(2-*N*-Phthalimidoethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

Diisopropyl azodicarboxylate (0.75 mL, 3.75 mmol) was added to a clear solution of 4-*N*-(2-hydroxyethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (1.2 g, 2.5 mmol), triphenylphosphine (1 g, 3.75 mmol) and phthalimide (560 mg, 3.75 mmol) in tetrahydrofuran (25 mL) at rt. After stirring at rt for 3 hours, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica, hexanes/ethyl acetate 70/30 to 50/50) to give the title compound; Rf = 0.55 (silica, hexanes/ethyl acetate 50/50).

Example 81 Preparation of compound of formula 4
4-*N*-(2-aminoethyl)phenylamino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine

A mixture of 4-*N*-(2-*N*-phthalimidoethyl)phenylamino-5-phenyl-7-(2,3-*O*-(methylethylidene)-β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (2.76 g, 4.5 mmol) and 97% hydrazine (0.8 mL) in ethanol (25 mL) was refluxed for 2 hours. After cooling to rt, the white precipitate that formed during the reaction was filtered off and rinsed with ethanol. The combined filtrates were concentrated under reduced pressure and the residue was dissolved in 70% aqueous trifluoroacetic acid. After stirring at rt for 2 hours, the reaction mixture was concentrated under reduced pressure and azeotroped twice with water and twice with ethanol. The residue was purified by column chromatography (silica, dichloromethane/methanol/28% aqueous ammonium hydroxide 90/10/1 to 70/30/1) to provide the title compound; Rf = 0.3 (silica, dichloromethane/methanol 80/20).

Example 82 Preparation of compound of formula 1
4-*N*-(2-guanidinoethyl)phenylamino-5-phenyl-7-(β-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine : Table 1 #309

The title compound is made following the procedure of M. S. Bernatowicz *et al. J. Org. Chem.* 57, 2497 (**1992**).

Example 83 Preparation of the Representative Heterocycles

Heterocycles, as shown in Scheme 14, are made in the following manner.

A. Preparation of compound of formula 37 (2-Amino-3-cyano-4-phenylpyrrole)

To a solution of phenacyl chloride (500 g, 3.23 M) in dry *N,N*-dimethylformamide (600 mL) was added potassium phthalimide, (600 g, 3.23 M) in small portions. The resulting mixture was stirred at ambient temperature overnight. To this was added malononitrile (256 g, 3.88 M) in one lot followed by a 25 wt % solution of sodium methoxide in methanol (744 mL, 3.2 mol). The resulting mixture

was stirred at room temperature overnight. Ice-water (10.0 L) was added to the reaction mixture and stirring was continued at room temperature overnight. The precipitate formed was collected by filtration and washed with cold water (4.0 L). The off-white solid was stirred in toluene (3.0 L) and filtered. The solid was washed with toluene (300 mL) and dried under vacuum at 60 C overnight. Yield 298.56 g. m.p. 172-174° C.

B. Preparation of compound of formula 39 (5-Phenyl-4-*N*-(4-fluorophenyl)aminopyrrolo[2,3-d]pyrimidine)

A mixture of the compound of Examiple 39A (296.0 g, 1.62 mol) and triethylorthoformate (3.2 L) was refluxed for 1 h. The triethylorthoformate was distilled off under reduced pressure until the pot temperature reached 88° C. To the cooled reaction mixture hexane(3.0 L) was added with vigorous stirring. The contents of the vessel were cooled to 0° C and the off-white solid formed was collected by filtration and washed with hexane (2x500 mL) and dried under suction. Final drying was done in a high vacuum oven. Yield of the 2-ethoxymethylene-3-cyano-4-phenylpyrrole was 323.0 g (83%). m.p. 98-100° C.

The above material (100 g, 0.42 mol) was dissolved in 1,2-dichlorobenzene. 4-Fluoroaniline(60 mL, 0.62 mol) was added and the reaction mixture was heated to 125° C for 1 h. An additional 985 mL of 1,2-dichlorobenzene was added and the reaction temperature was raised to 140° C for 3 h. Upon cooling to 0° C the title compound precipitated as a yellow solid which was collected by filtration and dried under vacuum. Yield 66.0 g. m.p. 215- 218° C.

C. Preparation of compound of formula 39
4-*N*-(4-*N*,*N*-Dimethylaminomethylphenyl)amino-5-phenyl-pyrrolo[2,3-d]Pyrimidine

This compound was made by a route similar to Example 39B. Here, the fluoroaniline was replaced with 4-*N*,*N*-dimethylaminomethylaniline. m.p. 208-209° C.

D. Preparation of compound of formula 39

5-Phenyl-4-phenylaminopyrrolo[2.3-d]pyrimidine

This compound was made by a route similar to Example 39B. Here, the fluoroaniline was replaced by aniline. m.p. 208-209° C.

E. Preparation of compound of formula 39

4-*N*-(4-Fluorophenyl)amino-5-(4-fluorophenyl)pyrrolo[2.3-d]pyrimidine

This compound was made by a route similar to 70A, replacing phenacyl chloride by 4-fluorophenacyl chloride, followed by treatment with 4-fluoroaniline as in example 70B; m.p. 245-248 °C.

F. Preparation of compound of formula 39

4-*N*-(4-Chlorophenyl)amino-5-phenylpyrrolo[2.3-d]pyrimidine

This compound was made by a route similar to 70B by replacing 4-fluoroaniline by 4-chloroaniline.

G. Preparation of compound of formula 39

4-*N*-[4-(2-Hydroxyethyl)phenyl]amino-5-phenylpyrrolo[2.3-d]pyrimidine

This compound was made by a route similar to 70B by replacing 4-fluoroaniline by 4-aminophenethyl alcohol; m.p. 206-208 °C

H. Preparation of compounds of formula 42

Heterocycles as shown in scheme 15, were made according to the procedures described in Browne et al. U.S. Patent Application Serial No. 08/812/916.

I. Preparation of compound of formula 39

4-*N*-[(1,1,2-Trimethylpropyl)dimethylsilyloxymethyl]phenylamino-5-phenylpyrrolo[2.3-d]pyrimidine

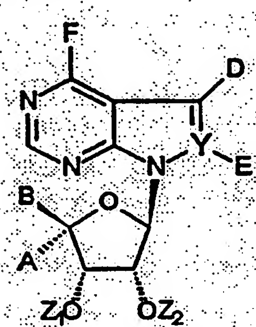
The title compound was prepared by a route similar to 70B by replacing 4-fluoroaniline by 4-aminobenzyl alcohol followed by silylation with dimethyl thexyl chlorosilane; Rf 0.5 (silica, hexanes/ethyl acetate 50/50).

Example 84

Representative C-4'-Symmetrically Substituted Pyrrolo Pyrimidine Nucleosides

Representative compounds of the invention, which can be made according to the methods described above, are identified in the following tables. With reference to Formula 1, preferred compounds of the invention are pyrrolo pyrimidines (Y is carbon) where the A and B substituents are the same.

In one group of preferred compounds A and B are both $HOCH_2$; in another, A and B are both hydrogen. G is preferably hydrogen, and E is preferably hydrogen or bromine, most preferably hydrogen. Z_1 and Z_2 are preferably hydrogen or methyl, most preferably hydrogen.



FORMULA 1

TABLE 1 C-4'-SYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES			
$Y = C \quad E = G = Z_1 = Z_2 = H$			
A=B=$HOCH_2$	A=B=H	F	D
1	27	phenylamino	phenyl
2	28	4-fluorophenylamino	phenyl
3	29	4-fluorophenylamino	4-fluorophenyl
4	30	4-fluorophenylamino	4-hydroxyphenyl
5	31	4-hydroxyphenylamino	phenyl
6	32	4-hydroxymethylphenylamino	phenyl
7	33	4-fluorophenylamino	3-pyridyl
8	34	3-pyridylamino	phenyl
9	35	phenylmethylamino	phenyl
10	36	4-(dimethylaminomethyl) phenylamino	phenyl

TABLE 1			
C-4'-SYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES			
$Y = C \quad E = G = Z_1 = Z_2 = H$			
$A=B=HOCH_2$	A = B = H	F	D
11	37	4-(*N,N*-diethylethylenediamino ethyl)-phenylamino	phenyl
12	38	4-fluorophenylamino	4-(2-dimethylaminoethyl)phenyl
13	39	4-cyanophenylamino	phenyl
14	40	4-fluorophenylamino	4-cyanophenyl
15	41	4-(2-dimethylaminoethyl carbamoyl)phenylamino	phenyl
16	42	4-(4-morpholinomethyl)phenyl amino	phenyl
17	43	4-(2-(1-piperazino)ethyl)phenylamino	phenyl
18	44	4-fluorophenylamino	4-(1-piperazinomethyl)phenyl
19	45	4-(sulfonamido)phenylamino	phenyl
20	46	4-(*N*-trifluoromethanesulfonyl amino)-phenylamino	phenyl
21	47	4-fluorophenylamino	4-(*N*-trifluoromethanesulfonylami no) phenyl
22	48	4-guanidinophenylamino	phenyl
23	49	4-fluorophenylamino	4-guanidinophenyl
24	50	4-(guanidinomethyl)phenylamino	phenyl
25	51	4-amidinophenylamino	phenyl
26	52	4-fluorophenylamino	4-amidinophenyl
267	299	4-chlorophenylamino	phenyl
268	300	amino	iodo
269	301	4-(2-(4-morpholino)ethyl)phenylamino	phenyl
270	302	4-fluorophenyl	4-(2-(1-piperazino)ethyl)phenyl
271	303	4-(diethylaminomethyl)phenylamino	phenyl
272	304	4-(1-piperazinomethyl)phenylamino)	phenyl
273	305	4-(1-piperidinoethyl)phenylamino	phenyl
274	306	4-(1-pyrrolidinoethyl)phenylamino	phenyl
275	307	4-(diethylcarboxamido)phenylamino	phenyl
276	308	4-(guanidinocarbonyl)phenylamino	phenyl
277	309	4-(2-guanidinoethyl)phenylamino	phenyl

TABLE 1

C-4'-SYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES

Y = C E = G = Z_1 = Z_2 = H

A=B=HOCH$_2$	A=B= H	F	D
278	310	4-(1-piperazinoacetyl)phenylamino	phenyl
279	311	4-(guanidinoacetyl)phenylamino	phenyl
280	312	4-(2-(1-tetrazolyl)ethyl)phenylamino	phenyl
281	313	4-fluorophenylamino	4-(5-tetrazolylmethyl)phenyl
282	314	4-(1-triazolylmethyl)phenylamino	phenyl
283	315	4-(1-imidazolylmethyl)phenylamino	phenyl
284	316	4-methoxyphenylamino	phenyl
285	317	4-ethoxyphenylamino	phenyl
286	318	4-(methylethyl)oxyphenylamino	phenyl
287	319	3-methoxyphenylamino	phenyl
288	320	4-fluorophenylamino	4-methoxyphenyl
289	321	4-fluorophenylamino	3-ethoxyphenyl
290	322	4-methoxyphenylamino	4-methoxyphenyl
291	323	4-ethoxyphenylamino	3-methoxyphenyl
292	324	3,4-methylenedioxyphenylamino	phenyl
293	325	4-ethoxyphenylamino	4-methylphenyl
294	326	4-methylphenylamino	phenyl
295	327	3-ethylaminophenylamino	phenyl
296	328	4-(methylethyl)phenylamino	phenyl
297	329	4-fluorophenylamino	4-methyl
298	330	4-fluorophenyl	3-guanidinophenyl
447	467	3,4-dimethoxyphenylamino	phenyl
448	468	3,4,5-trimethoxyphenylamino	phenyl
449	469	4-fluorophenylamino	3,4-dimethoxyphenyl
450	470	4-fluorophenylamino	3,4-ethylenedioxyphenyl
451	471	4-(2-methoxyethyloxy)phenylamino	phenyl
452	472	3-ethoxy-4-fluorophenylamino	phenyl

TABLE 1			
C-4'-SYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES			
Y = C E = G = Z_1 = Z_2 = H			
A=B=$HOCH_2$	A=B=H	F	D
453	473	3-aminophenylamino	phenyl
454	474	3-amino-4-fluorophenylamino	phenyl
455	475	4-fluorophenylamino	3-aminophenyl
456	476	3-ethylaminophenylamino	phenyl
457	477	3-diethylaminophenylamino	phenyl
458	478	4-fluorophenylamino	cyclohexyl
459	479	5-benzimidazolylamino	phenyl
460	480	4-(2-diethylaminoethyloxy)phenylamino	phenyl
461	481	4-(2-carboxyethyl)phenylamino	phenyl
462	482	4-(2-carboxyethenyl)phenylamino	phenyl
463	483	4-carboxyphenylamino	phenyl
464	484	4-fluorophenyl	4-(2-carboxyethenyl)phenyl
465	485	4-(carboxymethyl)phenylamino	phenyl
466	486	4-(2-*N*-aminoguanidinoethyl)phenylamino	phenyl

When E is bromine and A and B are both $HOCH_2$ a preferred compound is one where **(53)** F is 4-fluorophenylamino and D is phenyl. Using the same definitions for D, E, F, G, and Z_1, Z_2, another preferred compound is one where **(54)** A and B are both hydrogen.

Example 76

Representative C-4' Unsymmetrically Substituted Pyrrolo Pyrimidine Nucleosides

Other prefered pyrolo pyrimidine compounds of the invention are those where A and B are not the same, as shown in Tables 2 and 3.

TABLE 2			
C-4'-UNSYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES			
Y = C E = G = Z_1 = Z_2 = H			
A=$HOCH_2$ B=CH_3	B=$HOCH_2$ A=CH_3	F	D
55	81	phenylamino	phenyl

TABLE 2 C-4'-UNSYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES $Y = C \quad E = G = Z_1 = Z_2 = H$			
A=$HOCH_2$ B=CH_3	B=$HOCH_2$ A=CH_3	F	D
56	82	4-fluorophenylamino	phenyl
57	83	4-fluorophenylamino	4-fluorophenyl
58	84	4-fluorophenylamino	4-hydroxyphenyl
59	85	4-hydroxyphenylamino	phenyl
60	86	4-hydroxymethylphenylamino	4-fluorophenyl
61	87	4-fluorophenylamino	3-pyridyl
62	88	3-pyridylamino	phenyl
63	89	phenylmethylamino	phenyl
64	90	4-(dimethylaminomethyl) phenylamino	phenyl
65	91	4-(*N,N*-diethylethylenediamino ethyl)phenylamino	phenyl
66	92	4-fluorophenylamino	4-(2-dimethylaminoethyl)phenyl
67	93	4-cyanophenylamino	phenyl
68	94	4-fluorophenylamino	4-cyanophenyl
69	95	4-(2-dimethylaminoethyl carbamoyl)-phenylamino	phenyl
70	96	4-(4-morpholinomethyl)phenyl amino	phenyl
71	97	4-(2-(1-piperazino)ethyl)phenylamino	phenyl
72	98	4-fluorophenylamino	4-(1-piperazinomethyl)phenyl
73	99	4-(sulfonamido)phenylamino	phenyl
74	100	4-(*N*-trifluoromethanesulfonyl amino)-phenylamino	phenyl
75	101	4-fluorophenylamino	4-(*N*-trifluoromethane-sulfonyl amino)phenyl
76	102	4-guanidinophenylamino	phenyl
77	103	4-fluorophenylamino	4-guanidinophenyl
78	104	4-(guanidinomethyl)phenylamino	phenyl
79	105	4-amidinophenylamino	phenyl
80	106.	4-fluorophenylamino	4-amidinophenyl

When E is bromine, A is $HOCH_2$ and B is CH_3, a preferred compound is one where **(107)** F is 4-fluorophenylamino and D is phenyl. Using the same definitions

for D, E, F, G, and Z_1, Z_2, another preferred compound is one where **(108)** A is CH_3 and B is $HOCH_2$.

Example 77

Additional C-4' Unsymmetrically Substituted Pyrrolo Pyrimidine Nucleosides

Still other prefered pyrolo pyrimidine compounds of the invention are those where one of A and B is CH_3 and the other is CH_2NH_2, or one of A and B is methoxymethyl or CH_2OH, or one of A and B is CH_2OH and CH_2NH_2 as shown in Table 3.

TABLE 3

MORE C-4'-UNSYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES

Y = C E = G = Z_1 = Z_2 = H			
A=CH_3 B=H_2NCH_2	A=H_2NCH_2 B=CH_3	F	D
109	128	phenylamino	phenyl
110	129	4-chlorophenylamino	phenyl
111	130	4-fluorophenylamino	4-fluorophenyl
112	131	4-fluorophenylamino	4-hydroxyphenyl
113	132	4-hydroxyphenylamino	phenyl
114	133	4-hydroxymethylphenylamin o	phenyl
115	134	phenylamino	3-pyridyl
116	135	3-pyridylamino	phenyl
117	136	phenylmethylamino	phenyl
118	137	4-cyanophenylamino	phenyl
119	138	4-fluorophenylamino	4-cyanophenyl
120	139	4- carbamoylphenylamino	phenyl
121	140	4-(sulfonamido)phenylamino	phenyl
122	141	4-(*N*-trifluoromethanesulfony l amino)phenylamino	phenyl
123	142	phenylamino	4-(*N*-trifluoromethanesulfonylamin o) phenyl
124	143	4-guanidinophenylamino	phenyl
125	144	4-fluorophenylamino	4-guanidinophenyl
126	145	4-amidinophenylamino	phenyl

TABLE 3

MORE C-4'-UNSYMMETRICALLY SUBSTITUTED PYRROLO PYRIMIDINE NUCLEOSIDES

Y = C E = G = Z_1 = Z_2 = H			
A=CH_3 B=H_2NCH_2	A=H_2NCH_2 B=CH_3	F	D
127	146	4-fluorophenylamino	4-amidinophenyl
331	332	4-fluorophenylamino	phenyl
A=CH_3OCH_2 B=$HOCH_2$	A=$HOCH_2$ B=CH_3OCH_2	F	D
333	353	phenylamino	phenyl
334	354	4-chlorophenylamino	phenyl
335	355	4-fluorophenylamino	4-fluorophenyl
336	356	4-fluorophenylamino	4-hydroxyphenyl
337	357	4-hydroxyphenylamino	phenyl
338	358	4-hydroxymethylphenylamino	phenyl
339	359	phenylamino	3-pyridyl
340	360	3-pyridylamino	phenyl
341	361	phenylmethylamino	phenyl
342	362	4-cyanophenylamino	phenyl
343	363	4-fluorophenylamino	4-cyanophenyl
344	364	4- carbamoylphenylamino	phenyl
345	365	4-(sulfonamido)phenylamino	phenyl
346	366	4-(*N*-trifluoromethanesulfonyl amino)phenylamino	phenyl
347	367	phenylamino	4-(*N*-trifluoromethanesulfonylamino) phenyl
348	368	4-guanidinophenylamino	phenyl
349	369	4-fluorophenylamino	4-guanidinophenyl
350	370	4-amidinophenylamino	phenyl
351	371	4-fluorophenylamino	4-amidinophenyl
352	372	4-fluorophenylamino	phenyl
A=H_2NCH_2 B=$HOCH_2$	A=$HOCH_2$ B=H_2NCH_2	F	D
373	393	phenylamino	phenyl
374	394	4-chlorophenylamino	phenyl
375	395	4-fluorophenylamino	4-fluorophenyl
376	396	4-fluorophenylamino	4-hydroxyphenyl

A=H_2NCH_2 B=$HOCH_2$	A=$HOCH_2$ B=H_2NCH_2	F	D
377	397	4-hydroxyphenylamino	phenyl
378	398	4-hydroxymethylphenylamino	phenyl
379	399	phenylamino	3-pyridyl
380	400	3-pyridylamino	phenyl
381	401	phenylmethylamino	phenyl
382	402	4-cyanophenylamino	phenyl
383	403	4-fluorophenylamino	4-cyanophenyl
384	404	4- carbamoylphenylamino	phenyl
385	405	4-(sulfonamido)phenylamino	phenyl
386	406	4-(*N*-trifluoromethanesulfonyl amino)phenylamino	phenyl
387	407	phenylamino	4-(*N*-trifluoromethanesulfonylamino) phenyl
388	408	4-guanidinophenylamino	phenyl
389	409	4-fluorophenylamino	4-guanidinophenyl
390	410	4-amidinophenylamino	phenyl
391	411	4-fluorophenylamino	4-amidinophenyl
392	412	4-fluorophenylamino	phenyl

When E is bromine, A is NH_2CH_2 and B is CH_3, a preferred compound is one where **(147)** F is 4-fluorophenylamino and D is phenyl. Using the same definitions for D, E, F, G, and Z_1, Z_2, another preferred compound is one where **(148)** A is CH_3 and B is NH_2CH_2.

Example 78

Representative C-4' Spirocyclic Pyrrolo Pyrimidine Nucleosides

A and B can together form a cyclopropyl ring. Prefered pyrolo compounds of this kind, where E, G, Z_1 and Z_2 are all hydrogen, are shown in Table 4.

TABLE 4 C-4' SPIROCYCLIC PYRROLO PYRIMIDINE NUCLEOSIDES		
A & B FORM A RING Y = C E = G = Z_1 = Z_2 = H		
	F	D
149	phenylamino	phenyl
150	4-fluorophenylamino	phenyl

TABLE 4 C-4' SPIROCYCLIC PYRROLO PYRIMIDINE NUCLEOSIDES		
A & B FORM A RING Y = C E = G = Z_1 = Z_2 = H		
	F	D
151	4-fluorophenylamino	4-fluorophenyl
152	4-fluorophenylamino	4-hydroxyphenyl
153	4-hydroxyphenylamino	phenyl
154	4-hydroxymethylphenylamino	4-fluorophenyl
155	4-fluorophenylamino	3-pyridyl
156	3-pyridylamino	phenyl
157	phenylmethylamino	phenyl
158	4-(dimethylaminomethyl)phenylamino	phenyl
159	4-(*N,N*-diethylethylenediaminoethyl)phenyl amino	phenyl
160	4-fluorophenylamino	4-(2-dimethylaminoethyl)phenyl
161	4-cyanophenylamino	phenyl
162	4-fluorophenylamino	4-cyanophenyl
163	4-(2-dimethylaminoethylcarbamoyl)-phenylamino	phenyl
164	4-(4-morpholinomethyl)phenylamino	phenyl
165	4-(2-(1-piperazino)ethyl)phenylamino	phenyl
166	4-fluorophenylamino	4-(1-piperazinomethyl)phenyl
167	4-(sulfonamido)phenylamino	phenyl
168	4-(*N*-trifluoromethanesulfonylamino)phenyl amino	phenyl
169	4-fluorophenylamino	4-(*N*-trifluoromethanesulfonylamino) phenyl
170	4-guanidinophenylamino	phenyl
171	4-fluorophenylamino	4-guanidinophenyl
172	4-(guanidinomethyl)phenylamino	phenyl
173	4-amidinophenylamino	phenyl
174	4-fluorophenylamino	4-amidinophenyl
175	amino	iodo

TABLE 4a C-4' SPIROAZETIDINO PYRROLOPYRIMIDINE NUCLEOSIDES		
Y = C E = G = Z_1 = Z_2 = H		
A & B Form a ring containing a nitrogen	F	D
413	phenylamino	phenyl
414	4-fluorophenylamino	phenyl

TABLE 4a C-4' SPIROAZETIDINO PYRROLOPYRIMIDINE NUCLEOSIDES		
Y = C E = G = Z_1 = Z_2 = H		
A & B Form a ring containing a nitrogen	F	D
415	4-fluorophenylamino	4-fluorophenyl
416	4-fluorophenylamino	4-hydroxyphenyl
417	4-hydroxyphenylamino	phenyl
418	4-hydroxymethylphenylamino	phenyl
419	phenylamino	3-pyridyl
420	3-pyridylamino	phenyl
421	phenylmethylamino	phenyl
422	4-cyanophenylamino	phenyl
423	4-fluorophenylamino	4-cyanophenyl
424	4- carbamoylphenylamino	phenyl
425	4-(sulfonamido)phenylamino	phenyl
426	4-(*N*-trifluoromethanesulfonyl amino)phenylamino	phenyl
427	phenylamino	4-(*N*-trifluoromethanesulfonylamin o) phenyl
428	4-guanidinophenylamino	phenyl
429	4-fluorophenylamino	4-guanidinophenyl
430	4-amidinophenylamino	phenyl
431	4-fluorophenylamino	4-amidinophenyl

When E is bromine, and A and B form a cyclopropyl ring, a preferred compound is one where **(176)** F is 4-fluorophenylamino and D is phenyl.

<u>Example 79</u>

<u>Representative C-4' Symmetrically Substituted Pyrazolo Pyrimidine Nucleosides</u>

An additional group of prefered compound are the pyrazolo pyrimidines, where Y is nitrogen and E is nothing. Representative gem pyrazolo compounds, where A and B are the same (in this case both hydrogen) are shown in Table 5.

TABLE 5

C-4' SYMMETRICALLY SUBSTITUTED PYRAZOLO PYRIMIDINE NUCLEOSIDES

$Y = N \quad G = Z_1 = Z_2 = H$

A=B=H	F	D
177	phenylamino	phenyl
178	4-fluorophenylamino	phenyl
179	4-fluorophenylamino	4-fluorophenyl
180	4-fluorophenylamino	4-hydroxyphenyl
181	4-hydroxyphenylamino	phenyl
182	4-hydroxymethylphenylamino	4-fluorophenyl
183	4-fluorophenylamino	3-pyridyl
184	3-pyridylamino	phenyl
185	phenylmethylamino	phenyl
186	4-(dimethylaminomethyl)phenylamino	phenyl
187	4-(*N,N*-diethylethylenediaminoethyl) phenylamino	phenyl
188	4-fluorophenylamino	4-(2-dimethylaminoethyl)phenyl
189	4-cyanophenylamino	phenyl
190	4-fluorophenylamino	4-cyanophenyl
191	4-(2-dimethylaminoethyl carbamoyl)-phenylamino	phenyl
192	4-(4-morpholinomethyl)phenylamino	phenyl
193	4-(2-(1-piperazino)ethyl)phenylamino	phenyl
194	4-fluorophenylamino	4-(1-piperazinomethyl)phenyl
195	4-(sulfonamido)phenylamino	phenyl
196	4-(*N*-trifluoromethanesulfonylamino) phenylamino	phenyl
197	4-fluorophenylamino	4-(*N*-trifluoromethanesulfonylamino) phenyl
198	4-guanidinophenylamino	phenyl
199	4-fluorophenylamino	4-guanidinophenyl
200	4-(guanidinomethyl)phenylamino	phenyl
201	4-amidinophenylamino	phenyl
202	4-fluorophenylamino	4-amidinophenyl
432	phenylamino	4-chlorophenyl
433	4-methoxyphenylamino	phenyl
434	4-ethoxyphenylamino	phenyl
435	4-(methylethyl)oxyphenylamino	phenyl

TABLE 5 C-4' SYMMETRICALLY SUBSTITUTED PYRAZOLO PYRIMIDINE NUCLEOSIDES		
$Y = N \quad G = Z_1 = Z_2 = H$		
A=B=H	F	D
436	3-methoxyphenylamino	phenyl
437	4-fluorophenylamino	4-methoxyphenyl
438	4-fluorophenylamino	3-ethoxyphenyl
439	4-methoxyphenylamino	4-methoxyphenyl
440	4-ethoxyphenylamino	3-methoxyphenyl
441	3,4-methylenedioxyphenylamino	phenyl
442	4-ethoxyphenylamino	4-methylphenyl
443	4-methylphenylamino	phenyl
444	3-ethylaminophenylamino	phenyl
445	4-(methylethyl)phenylamino	phenyl
446	4-fluorophenylamino	4-methyl

Example 80

C-4' Unsymmetrically Substituted Pyrazolo Pyrimidine Nucleosides

Still other prefered pyrazolo pyrimidine compounds of the invention are those where one of A and B is CH_3 and the other is H_2NCH_2, as shown in Table 6.

TABLE 6 C-4' UNSYMMETRICALLY SUBSTITUTED PYRAZOLO PYRIMIDINE NUCLEOSIDES			
$Y = N \quad G = Z_1 = Z_2 = H$			
A=CH_3 B=H_2NCH_2	A=H_2NCH_2 B=CH_3	F	D
203	222	phenylamino	phenyl
204	223	4-fluorophenylamino	phenyl
205	224	4-fluorophenylamino	4-fluorophenyl
206	225	4-fluorophenylamino	4-hydroxyphenyl
207	226	4-hydroxyphenylamino	phenyl
208	227	4-hydroxymethylphenylamino	phenyl

TABLE 6 C-4' UNSYMMETRICALLY SUBSTITUTED PYRAZOLO PYRIMIDINE NUCLEOSIDES			
$Y = N \quad G = Z_1 = Z_2 = H$			
$A=CH_3$, $B=H_2NCH_2$	$A=H_2NCH_2$, $B=CH_3$	F	D
209	228	4-fluorophenylamino	3-pyridyl
210	229	3-pyridylamino	4-fluorophenyl
211	230	phenylmethylamino	phenyl
212	231	4-cyanophenylamino	phenyl
213	232	4-carbamoylphenylamino	phenyl
214	233	4-fluorophenylamino	4-cyanophenyl
215	234	4-(sulfonamido)phenylamino	phenyl
216	235	4-(*N*-trifluoromethanesulfonyl amino)-phenylamino	phenyl
217	236	4-fluorphenylamino	4-(*N*-trifluoromethanesulfonylamino) phenyl
218	237	4-guanidinophenylamino	phenyl
219	238	4-fluorophenylamino	4-guanidinophenyl
220	239	4-amidinophenylamino	phenyl
221	240	4-fluorophenylamino	4-amidinophenylamino

<u>Example 81</u>

<u>Representative C-4' Spirocyclic Pyrazolo Pyrimidine Nucleosides</u>

A and B can together form a cyclopropyl ring. Preferred pyrazolo pyrimidine nucleosides of this kind, where G, Z_1 and Z_2 are all hydrogen, are shown in Table 7.

TABLE 7 C-4' SPIROCYCLIC PYRAZOLO PYRIMIDINE NUCLEOSIDES		
A & B FORM A RING $Y = N \quad G = Z_1 = Z_2 = H$		
	F	D
241	phenylamino	phenyl
242	4-fluorophenylamino	phenyl
243	phenylamino	4-chlororophenyl
244	4-fluorophenylamino	4-hydroxyphenyl
245	4-hydroxyphenylamino	phenyl
246	4-methoxyphenylamino	phenyl

TABLE 7 C-4' SPIROCYCLIC PYRAZOLO PYRIMIDINE NUCLEOSIDES		
A & B FORM A RING Y = N G = Z_1 = Z_2 = H		
	F	D
247	4-hydroxymethylphenylamino	phenyl
248	4-fluorophenylamino	3-pyridyl
249	3-pyridylamino	phenyl
250	phenylmethylamino	phenyl
251	4-(dimethylaminomethyl)phenylamino	phenyl
252	4-(*N,N*-diethylethylenediaminoethyl) phenylamino	phenyl
253	4-fluorophenylamino	4-(2-dimethylaminoethyl)phenyl
254	4-cyanophenylamino	phenyl
255	4-fluorophenylamino	4-cyanophenyl
256	4-(2-dimethylaminoethylcarbamoyl)-phenylamino	phenyl
257	4-(4-morpholinomethyl)phenylamino	phenyl
258	4-(2-(1-piperazino)ethyl)phenylamino	phenyl
259	4-fluorophenylamino	4-(1-piperazinomethyl)phenyl
260	4-(sulfonamido)phenylamino	phenyl
261	4-(*N*-trifluoromethanesulfonylamino) phenylamino	phenyl
262	4-fluorophenylamino	4-(*N*-trifluoromethanesulfonylamino) phenyl
263	4-guanidinophenylamino	phenyl
264	4-fluorophenylamino	4-guanidinophenyl
265	4-(guanidinomethyl)phenylamino	phenyl
266	4-amidinophenylamino	phenyl

UTILITY

The adenosine kinase inhibitors of the present invention may be used in the treatment of a variety of clinical situations where increasing local levels of adenosine are beneficial. The compounds of the invention act as potent inhibitors of adenosine kinase in vitro, and the present compounds in particular are orally available.

Adenosine has been proposed to serve as a natural anticonvulsant. Compounds of the present invention which enhance adenosine levels are useful in seizure disorders, as shown in animal models of seizures detailed below. Adenosine kinase inhibitors may be used in the treatment of patients with seizures or epilepsy

or patients who might have chronic low or insufficient adenosine levels or might benefit from increased adenosine such as those suffering from autism, cerebral palsy, insomnia or other neuropsychiatric symptoms.

Adenosine kinase inhibitors of the invention find further utility in the treatment of acute pain, including but not limited to peri-operative, post-surgical, and end-stage cancer pain. Compounds of the invention are also useful in controlling chronic pain, including but not limited to pain caused by arthritis, cancer, trigeminal neuralgia, multiple sclerosis, neuropathies such as those arising from diabetes and AIDS and in addition, lower back pain and phantom limb pain. Treatment of acute and chronic pain can be treated by administration of the compounds of the invention in a systemic or oral fashion, as illustrated by animal models detailed below.

Adenosine has been reported to be an endogenous modulator of inflammation by virtue of its effects on stimulated neutrophil function and on macrophage, lymphocyte and platelet function. The compounds of this invention may therefore be used in treating conditions in which inflammatory processes are prevalent such as arthritis, reperfusion injury, and other inflammatory disorders.

The compounds of the invention are also useful in the treatment of chronic neurodegenerative disease, such as Alzheimer's disease, Parkinson's disease, ALS, Huntington's disease, and AIDS dementia.

Stroke and central nervous system ("CNS") trauma are conditions where tissue injury results from reduced blood supply to the CNS and are thus amenable to an intervention that provides increased levels of adenosine to the compromised tissue. It is reported that a significant component of the neurodegeneration resulting from stroke or CNS trauma is caused by increased excitatory amino acid release and sensitivity, which results in neurons being stimulated to death. In addition to vasodilatory properties, adenosine has been reported to inhibit release of excitatory amino acids (Burke and Nadler *J. Neurochem.*, 1988, 51:1541) and responsiveness of neurons to excitation. The compounds of this invention, which increase adenosine levels, may also be used in the treatment of conditions where release of or sensitivity to excitatory amino acids is implicated.

To assist in understanding the present inventions and especially their properties and utilities, the results of a series of experiments are also included. These experiments demonstrated that a number of compounds of the present invention were potent inhibitors of a purified cardiac adenosine kinase. Certain adenosine kinase inhibitors were found to inhibit seizures and exhibit anti-inflammatory activity in well-established animal models. The results of these experiments are shown in Table 8.

TABLE 8 UTILITY OF REPRESENTATIVE COMPOUNDS

#	Name	(IC_{50}) AK Inhibition (nM)	Carrageenan Paw (%inh)		Anticonvulsant Activity (MES) i.p. (mg/kg)
			p.o.	i.p.	
1	4-*N*-Phenylamino-5-phenyl-7-(4-*C*-hydroxymethyl-1-*β*-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 232 C)	1.2	18	3	>1.00
150	4-N-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-spirocyclopropyl-*β*-D-erythrofuranosyl)pyrrolo [2,3-d]pyrimidine (m.p. 142 C)	0.3	80	78	0.23
175	4-Amino-5-iodo-7-(4-*C*-spirocyclopropyl-*β*-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 232 C)	600			
81	4-*N*-Phenylamino-5-phenyl-7-(4-*C*-methyl-B-D-ribfuranosyl) pyrrolo[2,3-d]pyrimidine (m.p. 211-213 C)	2000			
64	4-*N*-(4-(Dimethylamino methyl)phenyl]amino-5-phenyl-7-(4-*C*-methyl-B-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 205-206 C)	70			>5.0
27	4-*N*-Phenylamino-5-phenyl-7-(*β*-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 210-211 C)	4	12	44	<5.0
372	4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-methoxymethyl-*β*-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 205-206 C)	24			>5.0
352	4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-C-methoxymethyl-b-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 198-199 C)	400			

TABLE 8	UTILITY OF REPRESENTATIVE COMPOUNDS				
#	Name	(IC_{50}) AK Inhibition (nM)	Carrageenan Paw (%inh)		Anticonvulsant Activity (MES) i.p. (mg/kg)
			p.o.	i.p.	
392	4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4-*C*-aminomethyl-b -D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine dihydrochloride (m.p. 200-220 C dec)	1100			
432	3-(4-Chlorophenyl)-1-(b-D-erythrofuranosyl)-4-*N*-phenylaminopyrazolo[3,4-d]pyrimidine (m.p. 194-195 C)	90	15	24	>5.0
28	4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(b-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 194-195 C)	28	25	52	<5.0
29	4-*N*-(4-Fluorophenyl)amino-5-(4-fluorophenyl)-7-(b-D-erythrofuranosylpyrrolo[2,3-d]pyrimidine (m.p. 200-202 C)	45	20	46	
299	4-*N*-(4-Chlorophenyl)amino-5-phenyl-7-(b-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 212-213 C)	40	28	20	
300	4-Amino-5-iodo-7-(b-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 258 C (dec.))	6	91	90	
301	4-*N*-[4-(2-(4-Morpholino)ethyl)phenyl]amino-5-phenyl-7-(b-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine (m.p. 128-130 C)	1	39	21	
43	4-*N*-[4-(2-(1-Piperazino)ethyl)phenyl]amino-5-phenyl-7-(b-D-erythrofuranosyl)pyrrolo[2,3-d]pyrimidine trihydrochloride (m.p. 150-180 (dec.))	3.5	34	65	

AK INHIBITION

Adenosine kinase activity was measured essentially as described by Yamada *et al.* (Yamada, Y., Goto, H., Ogasawara, N. (1988) *Biochim. Biophys. Acta* 660, 36-43.) with a few minor modifications. Assay mixtures contained 50 mM TRIS-maleate buffer, pH 7.0, 0.1% BSA, 1 mM ATP 1 mM $MgCl_2$, 0.5 μM [U-^{14}C] adenosine (400-600 mCi/mmol) and varying duplicate concentrations of inhibitor. The reactions were initiated by addition of approximately 0.1 μU partially purified pig heart adenosine kinase or recombinant human adenosine kinase (Spychala, J. et al., *Proc.Natl.Acad.Sci. USA 93,* 1232-1237, (1996)), where one unit is defined as that amount of enzyme required to phosphorylate 1 μmol adenosine per minute. The reactions were incubated for 20 minutes at 37° C. The assay was quenched upon spotting 30 μL aliquots onto 2 cm^2 pieces of Whatman DE81 anion exchange paper. The papersquares were washed for 3 minutes in 6 L distilled/deionized water to remove the unreacted adenosine. The washed squares were rinsed in 95% ethanol and dried in an oven at 100°C for 10 minutes. The amount of ^{14}C-AMP was quantified by scintillation counting. The concentration of inhibitor required to inhibit 50% of the adenosine kinase activity (IC_{50}) was determined graphically. The results for representative adenosine kinase inhibitors of the invention are shown in Table 8.

ANTICONVULSANT ACTIVITY

The anticonvulsant activity of the tested compounds was evaluated in male SA rats (100-150g, Simonsen) using the maximal electroshock (MES) model described in Swinyard et al., *Antiepileptic Drugs, 3d Ed.* at 85-102 (Levy, et al., eds.), NY: Raven Press (1989). The rats were maintained on a 12/12 light/dark cycle in temperature controlled facilities with free access to food and water. For p.o. administration, the animals are fasted overnight, prior to the experiment. One hour prior to seizure testing, the animals were injected interperitoneally (ip) or orally (*per os*, po) with one of various doses of test compound dissolved in DMSO or PEG 400.

Maximal electroshock seizures (MES) were induced by administering a 150 mA, 60 Hz current for 0.2 seconds via corneal electrodes using a Wahlquist

Model H stimulator. The endpoint measurement was suppression of hind limb tonic extension (HTE), which was judged to occur when any hind leg extension did not exceed a 90 degree angle with the plane of the body. HTE suppression of this kind indicates that the test compound has the ability to inhibit seizures, in theory by inhibiting seizure propagation and spread, if not by raising the seizure threshold (*i.e.* preventing seizure potential). This endpoint was expressed as the percentage of animals in which the response was inhibited. Typically, compounds were screened initially at one hour following a dose of 5 mg/kg ip. In some cases, the effective dose at which 50% of the rats were protected (ED_{50}) was calculated from a dose response curve. The results for exemplary compounds of the invention are set forth in Table 8, expressed as ED_{50} values. For compounds where the ED_{50} was not calculated, the result is listed as >5 if HTE was inhibited in fewer than 50% of the animals in the intial screen, or <5 if HTE was inhibited in more than 50% of the animals in the intial screen.

ANTI-INFLAMMATORY ACTIVITY

Carrageenan (Type λ) was suspended in sterile PBS at 1% (w/v), autoclaved for 30 minutes, and stored at room temperature. Rats were pretreated with vehicle or AK inhibitor (10 mg/kg) by oral gavage or i.p. administration and the volume of the left hind paw was measured using a water displacement plethysmometer (Stoelting Co., Wood Dale, IL). One hour after oral treatment or 30 minutes after i.p. treatment, the rats were briefly anaesthetized, and 0.1 ml of the carrageenan solution was injected subcutaneously into the planar surface of the left hind paw. The ensuing paw swelling was measured by plethysmometry after 3 hours. The paw volume in milliliters was subtracted from the pre-injection paw volume. Data are presented in Table 8 as the percent inhibition of paw swelling in AK inhibitor treated animals, compared to vehicle treated control animals. Rosengren et al., J. Immunology 154: 5444-51 (1995).

LIVER TOXICITY

Female SA rats (150-200 g) were anesthetized with halothane and cannulated via the internal jugular vein. The animals were allowed to recover for 3

days. At this time, 37.5 μmol/kg of an AK inhibitor was dissolved in 75% PEG400/25% saline and infused through the jugular catheter over 40 minutes. Twelve hours later, an additional 37.5 μmol kg was infused over 40 minutes (total dose = 75 μmol/kg). Twelve hours after the second dose, the animals were anesthetized with halothane and exsanguinated through the descending aorta. Serum was prepared and liver enzymes (serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT)) and total bilirubin in the serum samples were determined by a commercial laboratory. Results are shown in table 9.

TABLE 9: AVERAGE SERUM CONTENT OF SGOT, SGPT AND TOTAL BILIRUBIN

#	# animals	SGOT (U/mL)	SGPT (U/mL)	Total Bilirubin (U/mL)
1	2	65	53	0.1
150	2	560	155	1.58
27	5	114	41	0.14
28	4	61	23	0.07
29	4	130	30	0.16
43	5	99	58	0.1

RAT SKIN LESION MODEL

Rat skin lesions were induced as in Rosengren et al., J. Immunology 154: 5444-51 (1995). The dorsal skin of male SA rats was shaved and carrageenan (Type λ) or phosphate-buffered saline was injected intradermally. Three hours later, the injection sites were biopsied and weighed. Neutrophil content of the skin biopsies was measured as the quantity of myeloperoxidase (MPO) present in a tissue homogenate. The excised, weighed skin pieces were placed in 4 ml 0.5% mixed alkyl trimethylammonium bromide and homogenized at the highest speed for 15 seconds in a Polytron homogenizer (Brinkmann Instruments, Westbury, NY). Lipids were extracted by adding 1 ml of dichloromethane to the homogenate, vortexing

vigorously, and centrifuging at 1000g, 5°C for 15 min. Fifty μl of each supernatant was added in duplicate to a 96 well assay plate, along with dilutions of human myeloperoxidase standard. Potassium phosphate buffer (pH 6.1) containing 0.36 mg/ml of *o*-dianisidine dihydrochloride and 0.001% hydrogen peroxide was added (200 μl/well), and the absorbance at 450 nm was read after 5 min incubation at room temperature. The myeloperoxidase content of each skin piece was calculated from a standard curve constructed using least-square regression, and expressed as units of MPO/g of tissue.

AK inhibitors were administered orally using polyethylene glycol-400 as vehicle or intraperitoneally using dimethylsulfoxide as vehicle, at indicated time before skin lesion injection. For each experiment, the average of all values from saline-induced lesions was calculated. This baseline value was then subtracted from values obtained from carrageenan-induced lesions. Percent inhibition for AK inhibitors were calculated from these baseline-corrected values. The results are shown in Table 10.

TABLE 10 : Inhibition of neutrophil accumulation in rat skin lesions induced by carrageenan

#	# animals	Route	Pretreatment Time (min)	Dose (mg/kg)	% Inhibition	SEM
27	5	i.p.	30	3	2	14
27	5	i.p.	30	10	59	7
27	5	i.p.	30	30	89	2
27	8	i.p.	60	10	60	4
27	4	i.p.	120	10	14	6
27	4	i.p.	180	10	2	26
27	4	i.p.	240	10	0	
27	4	i.p.	360	10	0	
28	4	i.p.	30	3	18	10
28	12	i.p.	30	10	62	5
28	4	i.p.	30	30	79	11
28	8	i.p.	60	10	49	7
28	8	i.p.	120	10	60	4

28	8	i.p.	120	10	60	4
28	8	i.p.	240	10	28	8
28	8	p.o.	60	10	28	11
28	25	p.o.	60	20	40	7
28	10	p.o.	120	20	84	4
28	8	p.o.	240	20	77	4
28	8	p.o.	420	20	20	18
29	4	p.o.	60	10	0	
29	4	p.o.	60	20	26	15
29	3	p.o.	60	30	40	14

ADJUVANT ARTHRITIS

Heat-killed Mycobacterium butyricum was ground to a find powder and suspended in heavy mineral oil at 10 mg/ml. The suspension was injected subcutaneously into the base of the tail of male Lewis rats at 0.1 ml per rat. This immunization procedure induces an agressive arthritis that is apparent at day 10-12 and rapidly worsens. The volumes of the hind paws were measured before immunization and on days 12, 15 and 20 after immunization. The baseline paw volume was subtracted from the arthritic volumes to yield paw swelling. AK inhibitors were given by daily oral gavage beginning on day 4 after immunization, using polyethylene glycol-400 as the vehicle. Control rats received vehicle only. Percent inhibition was calculated based on paw swelling in AK inhibitor treated group compared to vehicle treated group, and is reported in Table 11.

TABLE 11: PERCENT INHIBITION

#	Dose (mg/kg)	% inh at day 12	% inh at day 15	% inh at day 20
28	10	29 ± 7	22 ± 4	-
28	20	52 ± 23	52 ± 22	40 ± 8

FORMALIN PAW

In this assay, injection of formalin, an irritant, into the hindpaw of rats typically evokes a biphasic response of pain-related behaviors. Phase 1 of the response which is brief, lasting approximately 0 - 5 min post-injection, is followed by a more prolonged phase 2, lasting approximately 10 - 80 min post-injection. Phase 1 behavior is thought to be a direct effect of the irritant on nociceptors at the injection site while phase 2 behavior is thought to include a hyperalgesic component mediated by sensitization of neuronal elements within the spinal cord. Studies from other laboratories have found the first portion of Phase 2 (sometimes referred to as Phase 2a) to be most responsive to pharmacological manipulation.

Rats (male, Simonsen) weighing between 100 - 200 g, are used in the present experiments. For screening purposes drugs are administered orally 90 min prior to initiation of formalin test. At designated intervals the animals in groups of 4 are placed individually in a small animal restrainer with the right hindpaw accessible through a hole in the bottom of the restrainer. The formalin paw assay is initiated by the injection using a 30G needle of 50 µl of a 5% formalin solution in saline into the right plantar surface of each hindpaw. The rat is then immediately placed in a separate plexiglass box and scoring (described below) of the animal's behavior is begun at 1.7 min after formalin injection. The instantaneous behavior of each animal in a group of 4 was observed and assigned a score once in each 20 second interval. This sequence is repeated over a 30 min period. The scoring protocol is an adaptation of the method published by Dubuisson and Dennis (Pain 4:161 -174, 1977) which assigns a score from 0 - 3 as follows:

0 - no discernible favoring of injected paw, weight evenly distributed
1 - injected paw is favored, rests lightly on floor
2 - injected paw is elevated
3 - injected paw is vigorously licked, bitten or shake

Scores are continuously recorded directly onto an Excel spreadsheet. For comparative examination of drug effects the data is reported in two different ways: 1) the scores are summed for Phase 1 (1.7 - 5 min post-formalin) and for

Phase 2 (10.3 - 30 min post-formalin) and the mean values of the sums are determined from 6 different animals with results expressed as % inhibition compared to vehicle control. 2) the total number of incidences specifically of licking/biting behavior is summed over Phase 2 and mean values determined from 6 different animals with results expressed as % inhibition compared to vehicle control. Results are shown in Table 12.

TABLE 12

IN VIVO ACTIVITY OF SELECTED AKIS IN RATS IN THE FORMALIN PAW MODEL

Example #	% Inhibition Phase 1 Composite score	% Inhibition Phase 2 Composite score	% Inhibition Phase 2 Licking/biting
27	25.5	47.6	77.5
28	9.2	37.4	76.1
29	24.8	35.1	67.8

FORMULATIONS

Compounds of the invention are administered to the affected tissue at the rate of from 0.1 to 200 nmole/min/kg, preferably from 1 to 50 nmol/min/kg. Such rates are easily maintained when soluble compounds are intravenously administered as discussed below. When other methods are used (e.g., oral administration), use of time-release preparations to control the rate of release of the active ingredient may be preferred. These compounds are administered in a dose of about 0.01 mg/kg/day to about 100 mg/kg/day, preferably from about 0.1 mg/kg/day to about 10 mg/kg/day.

For the purposes of this invention, the compounds of the invention may be administered by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters. Preferred for certain indications are methods of administration which allow rapid access to the tissue or

organ being treated, such as intravenous injections for the treatment of myocardial infarction. When an organ outside a body is being treated, perfusion is preferred.

Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including those from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene

oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadeaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension may also contain one or more preservative such as ethyl of n-propyl p-hydroxybenzoate, one or more coloring agent, one or more flavoring agent and one or more sweetening agent, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophylized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain 20 to 1000 μmoles of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions. It is preferred that pharmaceutical composition be prepared which provides easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion should contain from about 0.1 to about 15 μmoles of the active ingredient per ML of solution so that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

As noted above, formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by

compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach. This is particularly advantageous with the compounds of formula (I) as such compounds are susceptible to acid hydrolysis.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the ddPN ingredient such carriers as are known in the art to be appropriate.

Formations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be sorted in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior

to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

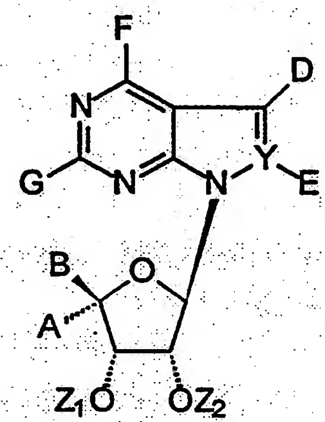
Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, or an appropriate fraction thereof, of an adenosine kinase inhibitor compound. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

Capsules comprising adenosine kinase inhibitors suitable for oral administration according to the methods of the present invention may be prepared as follows: (1) for a 10,000 capsule preparation: 1500 g of adenosine kinase inhibitor is blended with other ingredients (as described above) and filled into capsules which are suitable for administration depending on dose, from about 4 capsules per day (1 per 6 hours) to about 8 capsules per day (2 capsules per 6 hours), to an adult human.

The compounds of this invention and their preparation and use can be understood further by the representative examples above, which illustrate the various aspects of the invention without limiting its scope.

WE CLAIM:

1. C-4'-modified pyrrolo[2,3-d] and pyrazolo[3,4-d] pyrimidine nucleoside analogs of Formula 1



FORMULA 1

wherein:

A and B are both hydrogen, or are each independently alkenyl, the group $(CH_2)_nQ$, where n is from 1 to 4 and Q is hydrogen, hydroxy, alkyl, alkoxy, amino, azido, or halogen; or A and B together form a ring of from 3 to 6 carbons, the ring containing 0 to 3 heteroatoms selected from oxygen and nitrogen and optionally substituted by Q as defined above;

D is halogen, aryl, aralkyl, alkyl, alkenyl, alkynyl optionally containing one or more heteroatoms such as nitrogen, oxygen or sulfur, haloalkyl, cyano, or carboxamido;

E is nothing when Y is nitrogen; and is hydrogen, halogen, or alkyl when Y is carbon;

F is alkyl, aryl, aralkyl, halogen, amino, alkylamino, arylamino, aralkylamino, alkoxy, aryloxy, aralkyloxy, alkylthio, arylthio, aralkylthio;

G is hydrogen or halogen;

Y is carbon or nitrogen;

Z_1 and Z_2 are independently hydrogen, acyl, or taken together form a cyclic carbonate;

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, where Y is carbon.

3. A compound of claim 1, where Y is nitrogen.

4. A compound of any of claims 1-3 where A and B are the same.

5. A compound of any of claims 1-3 where A and B are the same, but are not both methyl.

6. A compound of any of claims 1-3 where A and B are both hydrogen.

7. A compound of any of claims 1-3 where A and B are different.

8. A compound of any of claims 1-3 where D is halogen, aryl, cyano, or CONRR', where R and R' are independently hydrogen or alkyl.

9. A compound of any of claims 1-3 where F is amino, arylamino, halogen or alkyl.

10. A compound of claim 1, where G and each Z are hydrogen.

11. A compound of claim 2, where E, G, and each Z are hydrogen.

12. A compound of claim 3, where G and each Z are hydrogen.

13. A compound of any of claims 10-12 where A and B are the same.

14. A compound of any of claims 10-12 where A and B are the same, but are not both methyl.

15. A compound of any of claims 10-12 where A and B are both hydrogen.

16. A compound of any of claims 10-12 where A and B are different.

17. A compound of any of claims 10-12 where D is aryl.

18. A compound of any of claims 10-12 where F is arylamino.

19. A compound of and of claims 1-3 where F is arylamino and D is aryl.

20. A compound of any of claims 10-12 where F is arylamino and D is aryl.

21. A compound of claim 1, where A and B together form a ring of 3 to 6 carbons, the ring containing 0 to 3 heteroatoms selected from oxygen and nitrogen and optionally substituted by hydrogen, hydroxy, alkyl, alkoxy, amino, azido or halogen.

22. A compound of claim 2, where A and B together form a ring of 3 to 6 carbons, the ring containing 0 to 3 heteroatoms selected from oxygen and nitrogen and optionally substituted by hydrogen, hydroxy, alkyl, alkoxy, amino, azido or halogen.

23. A compound of claim 3, where A and B together form a ring of 3 to 6 carbons, a ring containing 0 to 3 heteroatoms selected from oxygen and nitrogen and optionally substituted by hydrogen, hydroxy, alkyl, alkoxy, amino, azido or halogen.

24. A compound according to any of claims 21 and 23, where G and each Z are hydrogen.

25. A compound according to claim 22, where E, G and each Z are hydrogen.

26. A compound according to any of claims 21-23, where at least one of F is arylamino and D is aryl.

27. A compound according to any of claims 21-23, where F is arylamino and D is aryl.

28. A compound of claim 1, where A and B are independently $HOCH_2$ or CH_3, provided both A and B are not CH_3.

29. A compound of claim 2, where A and B are independently $HOCH_2$ or CH_3 provided both A and B are not CH_3.

30. A compound of claim 3, where A and B are independently $HOCH_2$ or CH_3 provided both A and B are not CH_3.

31. A compound of claim 28, where F is phenylamino optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl, and D is phenyl optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl.

32. A compound of claim 29, where F is phenylamino optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl, and D is phenyl optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl.

33. A compound of claim 30, where F is phenylamino optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl, and D is phenyl optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl.

34. A compound of claim 21, where F is phenylamino optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl, and D is phenyl optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl.

35. A compound of claim 22, where F is phenylamino optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl, and D is phenyl optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl.

36. A compound of claim 23, where F is phenylamino optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl, and D is phenyl optionally substituted at any position by halogen, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, amino, cyano or lower alkyl.

37. A compound according to any of claims 28-36 where G and each Z are hydrogen.

38. A compound according to any of claims 28, 29, 31, 32, 34, and 35 where E, G, and each Z are hydrogen.

39. A compound of claim 35, where D is phenyl and F is phenylamino substituted at any position by halogen or alkoxy.

40. A compound of claim 36, where D is phenyl and F is phenylamino substituted at any position by halogen or alkoxy.

41. A compound of any of claims 1-3 where D is halogen or aryl.

42. A compound of any of claims 1-3 where D is aryl.

43. A compound of any of claims 1-3 where F is amino or arylamino.

44. A compound of any of claims 1-3 where F is arylamino.

45. A compound of claim 6 where D is aryl.

46. A compound of claim 6 where F is arylamino.

47. A compound of claim 6 where D is aryl and F is arylamino.

48. A compound of claim 15 where D is aryl.

49. A compound of claim 15 where F is arylamino.

50. A compound of claim 15 where D is aryl and F is arylamino.

51. A compound of claim 6 where D is phenyl optionally substituted at any position by 1 to 2 substituents chosen independently from halogen, lower alkyl, amino, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6

membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally substituted by CONVV' where V and V' are independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms and optionally oxygen atoms, or V and V' together form a 6 membered ring containing at least one basic nitrogen.

52. A compound of claim 6 where F is is phenylamino optionally substituted at any position by 1 to 2 substituents chosen independently from halogen, lower alkyl, amino, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally substituted by CONVV' where V and V' are independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms and optionally oxygen atoms, or V and V' together form a 6 membered ring containing at least one basic nitrogen.

53. A compound of claim 6 where D is phenyl and F is phenylamino and both are optionally and independently substituted at any position by 1 to 2 substituents chosen independently from halogen, lower alkyl, amino, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally substituted by CONVV' where V and V' are independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms and optionally oxygen atoms, or V and V' together form a 6 membered ring containing at least one basic nitrogen.

54. A compound of claim 15 where D is phenyl optionally substituted at any position by 1 to 2 substituents chosen independently from halogen, lower alkyl, amino, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally substituted by CONVV' where V and V' are independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms and optionally oxygen atoms, or V and V' together form a 6 membered ring containing at least one basic nitrogen.

55. A compound of claim 15 where F is is phenylamino optionally substituted at any position by 1 to 2 substituents chosen independently from halogen, lower alkyl, amino, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally substituted by CONVV' where V and V' are independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms and optionally oxygen atoms, or V and V' together form a 6 membered ring containing at least one basic nitrogen.

56. A compound of claim 15 where D is phenyl and F is phenylamino and both are optionally and independently substituted at any position by 1 to 2 substituents chosen independently from halogen, lower alkyl, amino, hydroxy, alkoxy, perhalo lower alkyl, carboxamido, $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms, and optionally

substituted by CONVV' where V and V' are independently an alkyl chain, at least one of which contains one or more basic nitrogen atoms and optionally oxygen atoms, or V and V' together form a 6 membered ring containing at least one basic nitrogen.

57. A compound of claim 6 where D is phenyl optionally substituted by halogen.

58. A compound of claim 6 where F is phenylamino optionally substituted by halogen or $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms.

59. A compound of claim 6 where D is phenyl optionally substituted by halogen and F is phenylamino optionally substituted by halogen or $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms.

60. A compound of claim 15 where D is phenyl optionally substituted by halogen.

61. A compound of claim 15 where F is phenylamino optionally substituted by halogen or $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms.

62. A compound of claim 15 where D is phenyl optionally substituted by halogen and F is phenylamino optionally substituted by halogen or $(CH_2)_rT$ where r is from 0 to 3 and T is an alkyl chain of 0 to 16 carbon atoms containing one or more hetero atoms, N-sulfonylated amino, amidoximo, N-aminoguanidino, amidino, guanidino, acyl guanidino, cyclic derivatives of amidino, guanidino, aminoguanidino, 5 or 6 membered ring containing at least one basic nitrogen and optionally one or more oxygen atoms.

63. A compound of claim 6 where D is phenyl, 4-chlorophenyl or 4-fluorophenyl.

64. A compound of claim 15 where D is phenyl, 4-chlorophenyl or 4-fluorophenyl.

65. A compound of claim 58 where r is from 0 to 2 carbon atoms and T is one of amino, alkylamino, dialkylamino, guanidino, acyl guanidino, cyclic amidino, cyclic guanidino, an alicyclic ring containing at least one basic nitrogen and optionally one oxygen atom.

66. A compound of claim 61 where r is from 0 to 2 carbon atomsand T is one of amino, alkylamino, dialkylamino, guanidino, acyl guanidino, cyclic amidino, cyclic guanidino, an alicyclic ring containing at least one basic nitrogen and optionally one oxygen atom.

67. A compound of claim 6 where D is phenyl, 4-chlorophenyl or 4-fluorophenyl and F is phenylamino optionally substituted by halogen or $(CH_2)_rT$ where r is from 0 to 2 carbon atoms and T is one of amino, alkylamino, dialkylamino, guanidino, acyl guanidino, cyclic amidino, cyclic guanidino, an alicyclic ring containing at least one basic nitrogen and optionally one oxygen atom.

68. A compound of claim 15 where D is phenyl, 4-chlorophenyl or 4-fluorophenyl and F is phenylamino optionally substituted by halogen or $(CH_2)_rT$ where

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/10404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/14 C07H19/23 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 496 617 A (GENSIA PHARMA) 29 July 1992 see the whole document ---	1
A	US 4 904 666 A (FRIEBE WALTER-GUNAR ET AL) 27 February 1990 see the whole document -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 November 1996	26 -11- 1996

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/10404

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